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Aus der Städt. Kinderklinik Braunschweig (Leitender Arzt Dr. P. Dannenbaum) und dem Pathologischen Institut der Stadt Braunschweig (Leitender Arzt Dr R. Markworth)

Ein Beitrag zur Klinik und Morphologie der Letterer-Siweschen Erkrankung

von HERBERT SCHOLZ *und* JOACHIM SCHWARTZ

Das Bestreben, die Ursache der Retikulosen zu erkennen, führte zu einem Vergleich mit den Speicherkrankheiten. So wird besonders von Glanzmann, Wallgren, Farber, u. a. m. immer wieder betont, dass die Retikulose nur eine Variante der Lipoidgranulomatose sei, die ihrerseits als chronische Verlaufsform der Retikulose aufgefasst wird. Die Ähnlichkeit der röntgenologisch fassbaren Knochenerscheinungen schien für eine Identität zwischen Retikulose, eosinophilem Granulom und der Lipoidgranulomatose zu sprechen. Da sich in unserem Fall bei einem typischen histologischen Bild keinerlei Knochenveränderungen fanden, halten wir seine Mitteilung für angezeigt und geeignet, in die Diskussion über die Einordnung und die Ätiologie der Letterer-Siweschen Erkrankung einzutreten.

Es handelt sich um einen $4^1/_2$ Monate alten Säugling, der 2 Monate vor der Aufnahme mit einem Hautausschlag erkrankt war, welcher sich unter Salbenbehandlung nicht gebessert hatte. Seit einer Woche bestanden schlechter Appetit, vermehrte Unruhe, zeitweilig starker Husten und Kurzatmigkeit. Die ambulant angestellte Rö-Aufnahme der Lunge zeigte diffuse, kleinfleckige Infiltrate. Daraufhin erfolgte die Klinikeinweisung unter dem Verdacht einer Miliartuberkulose.

Der altersgemäss entwickelte, 5110 g schwere, männliche Säugling gelangte am 23.1. 51 in schwerstkrankem Zustand, hochgradig dyspnoisch und cyanotisch zur Aufnahme. — *Haut*: Am Rumpf, Brust, Bauch und Rücken, ebenso am Hals zahlreiche, symmetrisch angeordnete, petechiale und in den Hautfalten besonders dicht sitzende Blutungen (Faltenpurpura). Daneben eine Unzahl besonders am Rumpf lokalisierter, senfkorngrosser, perlmutterglänzender Knötchen. Die Haut fühlte sich im ganzen reibeisenartig an. Die Schleimhäute waren gut durchblutet und zeigten keine pathologischen Veränderungen. — Turgor und Muskeltonus waren normal. — *Nasen-Rachen-Raum* und *Ohren* unauffällig. — *Lunge:* Auskultatorisch über beiden Lungen mittel- bis feinblasige Rg., besonders über dem rechten Oberfeld. Keine Klopfschalldifferenzen. — *Herz:* Grenzen nicht verbreitert, Töne rein, Aktion regelmässig beschleunigt. — *Abdomen:* Leib weich, Leber $2^1/_2$ Querfinger unterhalb des

Abb. 1.

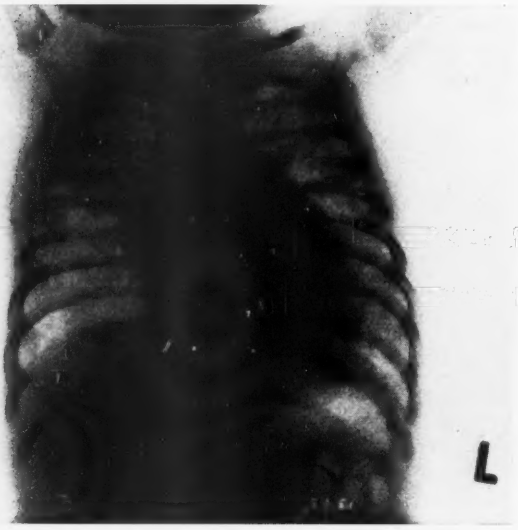

Abb. 2. Rö-Aufn. der Lunge: Diffuse, kleinfleckige Trübung beider Lungen mit besonderer Dichte im Bereich des rechten Oberlappens.

Rippenbogens, Milz nicht tastbar. — Keinerlei tastbare *Lymphknoten*schwellungen. — Extremitäten frei beweglich. Am *Skelettsystem* war klinisch kein krankhafter Befund zu erheben. Geringe Craniotabes, grosse Fontanelle $1^1/_2 \times 2$ Querfinger. — *ZNS*: Reflexe seitengleich und in normaler Stärke auslösbar, keine meningitischen Zeichen. — *Blutbild:* Hgb 88 %, 4,4 Ery., FI 1,0, 14 000 Leuko., 2 % Eo, 4 % Stab., 48 % Segm., 34 % Lympho., 12 % Mono., 110 000 Thrombocyten. Blutungszeit 4 Min., Gerinnungszeit 3 Min., BKS 8/16, Gesamtcholesterin 106 mg %, Blutkulturen steril. — *Urin* frei von pathologischen Bestandteilen. — *WaR* und Nebenreaktionen negativ.

tiv. *Tuberkulinproben* bis Mendel-Mantoux 1:100 negativ. Magenspülwasser frei von Tuberkelbazillen oder Tumorzellen. — *Temperaturen:* In den ersten Tagen zwischen 39° und 40°, dann kontinuierlich um 38°. — *Röntgenaufnahme der Lunge:* Diffuse, kleinfleckige Trübung beider Lungen mit besonderer Dichte im Bereich des rechten Oberlappens. — Die Röntgenuntersuchung des gesamten *Skelettsystems* einschliesslich des Schädels liess keine krankhaften Veränderungen, insonderheit keine herdförmigen Erscheinungen erkennen. — Am 14. Tag des Klinikaufenthaltes Exitus letalis unter den Zeichen des fortschreitenden Herzversagens.

Eine Miliartuberkulose, die anfangs auf Grund des röntgenologischen Lungenbefundes differentialdiagnostisch im Vordergrund stand und auch zu einer Streptomycinbehandlung Veranlassung gab, konnte bald durch die negativen Tuberkulinproben sowie durch ausbleibenden Bazillennachweis ausgeschlossen werden. — Da die Blutkulturen steril geblieben waren, war auch ein septisches Krankheitsgeschehen sehr unwahrscheinlich. — Eine Lues stand nach dem negativen Ergebnis der Seroreaktionen ausserhalb der Diskussion. — Eine Leukose kam auf Grund des Blutbildes nicht in Betracht. — Für eine Speicherkrankheit, wie die Schüller-Christiansche Erkrankung, sprach klinisch nichts. Auch ein Boecksches Sarkoid wurde differentialdiagnostisch erwogen. Die Röntgenaufnahme der Lunge liess auch an einen Tumor denken. Bei wiederholten Untersuchungen des Magenspülwassers konnten jedoch niemals Tumorzellen nachgewiesen werden. — Die rasche Zunahme der Hauterscheinungen und besonders die dichte Lokalisation der petechialen Blutungen in den Hautfalten stellten das von Letterer und Siwe beschriebene Krankheitsbild einer Retikuloendotheliose in den Vordergrund. Hier liess sich bei dem Alter des Kindes das klinische Bild mit seinen Haut- und Lungenerscheinungen, wie der Verlauf voll einordnen.

Für die nosologische Abgrenzung der Veränderungen des RS ist die feingewebliche Untersuchung aller veränderten Organe unbedingte Voraussetzung, weil ohne diese eine Differenzierung von klinisch ähnlichen Syndromen nicht möglich ist.

Sektionsbefund: Leiche eines 82 cm langen, 4900 g schweren, männlichen Kindes. *Haut:* An Brust, Bauch, Rücken, Hals und Hinterkopf und besonders in den Leistenbeugen, etwas auf die Oberschenkel übergreifend, finden sich zahlreiche, dichtstehende, flache Knötchen von durchschnittlich 1 mm Durchmesser. Auf der Kuppe tragen die Knötchen grösstenteils eine kleine bräunliche Kruste. Punktförmige Blutungen in den Ellenbeugen, Achselhöhlen und in der Haut beider Unterschenkel.

Zusammenfassend ergibt sich folgender pathologisch-anatomischer Befund: Hochgradige Purpura der Haut und knötchenförmige Effloreszenzen mit besonderer Lokalisation in den Leisten- und Ellenbeugen. — Hyper-

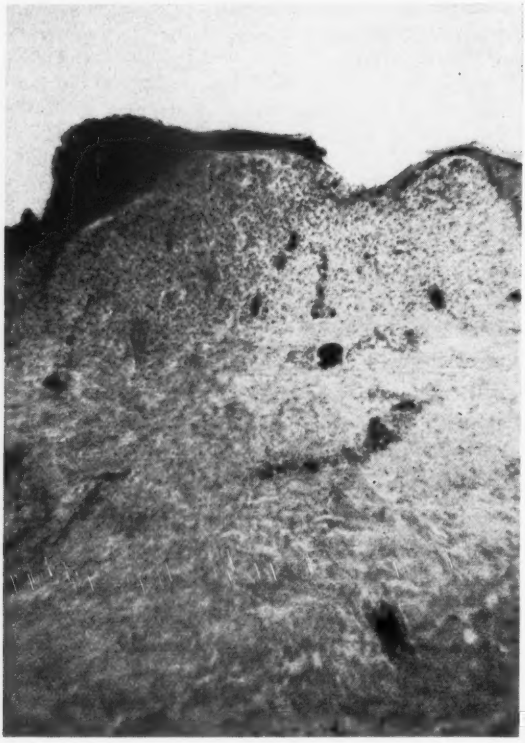

Abb. 3. Haut (Schnittpräparat in Haematox.-Eosin-Färbung): Knötchenförmige grosszellige Wucherung mit Schwund des Epithels. Grosszellige Wucherung der Adventitia der Blutgefässe.

plasie der Mesenterialwurzellymphknoten. — Interstitielle Pneumonie. Hochgradiges kollaterales Lungenemphysem. — Dilatation des parenchymgeschädigten Herzens. — Hochgradige Verfettung der Leber. Mässige Milzschwellung. Parenchymschädigung der Nieren.

Histologische Untersuchung: Folgende Färbungen wurden angewandt: Haematoxylin-Eosin, van Gieson, Scharlachrot, Azokarmin nach Heidenhain, Elastika nach Hart, Silberimprägnation nach Gömöri, sowie bei der Lunge die Fibrinfärbung nach Weigert.

Haut: In der Cutis finden sich grosszellige Wucherungen in Form flacher Knötchen. Das Epithel ist im Bereich dieser knötchenförmigen Eruptionen abgeflacht oder ganz geschwunden. An den Stellen mit völligem Epithelverlust finden sich Borken aus abgestorbenen Zellen. In den Randbezirken der Knötchen stellenweise kleine Blutungen. An den Gefässen der Cutis grosszellige Wucherungen der Adventitia.

Milz: Die normale Milzstruktur ist weitgehend aufgehoben. Die Follikel sind spärlich und klein. In der Pulpa finden sich zahlreiche Knötchen von der Grösse miliarer Tuberkel. Die Knötchen bestehen aus grossen Zellen mit einem grossen, hellen Plasmaleib und grossem ziemlich hellen Kern, der meistens ein Kernkörperchen enthält. Es handelt sich dabei um Wucherungen von Retikulumzellen. Nekrosen oder Lipoidablagerungen in den Knötchen sind nicht nachweisbar.

Mesenterialwurzellymphknoten: Das lymphatische Gewebe ist weitgehend einer überwiegend diffusen Wucherung von grossen Zellen des beschriebenen Typs gewichen. Teilweise sind die Wucherungen auch knötchenförmig. In den stärker vergrösserten Lymphknoten finden sich Nekrosen mit Einlagerungen von Lipoidsubstanzen. Die grossen, hellen Zellen zeigen keine Lipoideinlagerungen.

Lungen: Das Lungengewebe zeigt starke histiocytäre, grosszellige Wucherungen in den Alveolarsepten. In den stark verkleinerten Alveolen findet sich vielfach ein aus Leukocyten und Lymphocyten bestehendes Exsudat, das kein Fibrin enthält. Ausgedehnte Bezirke der Lungen sind durch diese Veränderungen stark verdichtet. Dazwischen befinden sich andere Bezirke mit einem grobblasigen Emphysem mit Schwund der Alveolarsepten.

Leber: Hochgradige, grobtropfige Verfettung der Leberzellen. Keine Vermehrung des interstitiellen Bindegewebes. Die Kapillaren sind stark mit Blutzellen ausgefüllt. Die Kupfferschen Sternzellen erscheinen teilweise etwas vergrössert.

Niere: Die Tubuli contorti zeigen Schwellung der Epithelien und Trübung des Protoplasmas. An den Glomeroli und Gefässen sind keine Veränderungen nachweisbar. Keine Verfettung der Tubulusepithelien.

Die von uns erhobenen Befunde entsprechen damit sehr weitgehend und im Prinzipiellen dem von LETTERER beschriebenen Bild der aleukämischen Retikulose. Herr Prof. LETTERER, dem unser besonderer Dank gilt, beurteilte unser Material und bestätigte unsere Diagnose.

Die Ätiologie der Retikulose ist noch ungeklärt. Wir können uns nicht der Ansicht GLANZMANNS und anderer Autoren anschliessen, dass es sich dabei um eine infektbedingte Erkrankung handelt. Alle angewandten Methoden, Erreger oder durch sie hervorgerufene Antikörper nachzuweisen, hatten ein negatives Ergebnis. Auch die Bakterienfärbung von Schnitten fiel negativ aus. Entzündliche Veränderungen waren nur an den Knötchen in der Haut nachweisbar, soweit sie die Epidermis durchbrochen hatten, und in den Lungen, und sind mit Sicherheit als sekundär entstanden anzusehen.

Die retikulär-histiocytären Wucherungen des RS, die in den verschiedenen Organen gefunden wurden, unterscheiden sich auch deutlich von Granulationsgewebe, auch von dem, das bei manchen Infektionskrankheiten (Typhus abdominalis, Lues, Tuberkulose usw.) gebildet wird.

Die Abgrenzung gegen die Lipoidgranulomatose ist schon dadurch gegeben, dass die Wucherungen des RS bei der Retikulose keine Lipoide speichern. Wir konnten in unserem Material Lipoide nur in den Nekrosen in den vergrösserten Mesenterialwurzellymphknoten finden. Die Lokalisa-

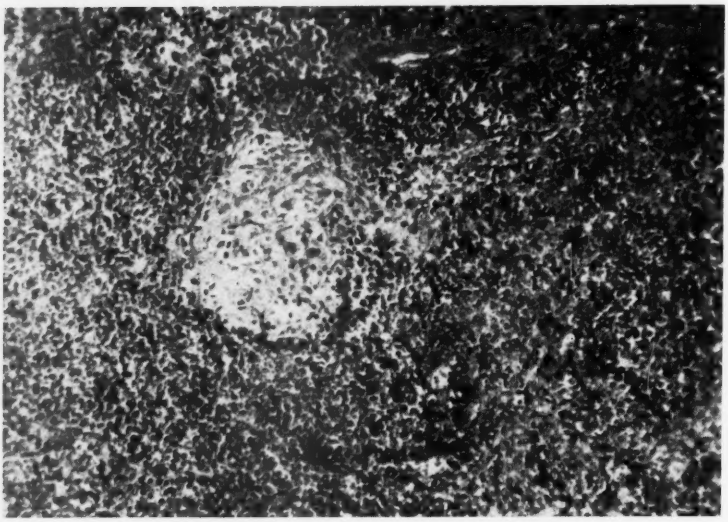

Abb. 4. Milz (Schnittpräparat in Haematox.-Eosin-Färbung): Milzstruktur aufgehoben. In der Pulpa rundliche Knötchen aus gewucherten Reticulumzellen mit grossem hellen Plasmaleib und grossem, ziemlich hellen Kern.

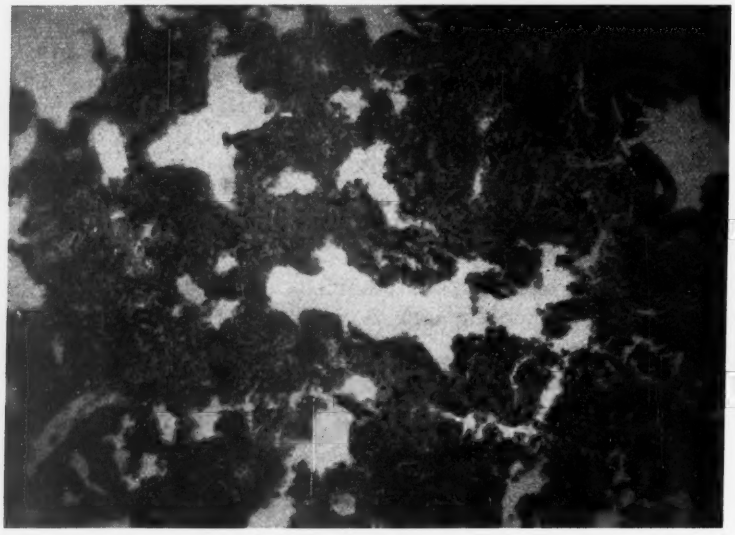

Abb. 5. Lunge (Schnittpräparat in Haematox.-Eosin-Färbung): Starke histiocytäre Wucherungen in den Alveolarsepten. In den Alveolen Exsudat aus Leucocyten und Lymphocyten. Daneben Bezirke mit grobblasigem Emphysem.

tion der Herde bei der Lipoidgranulomatose unterscheidet sich in den meisten Fällen wesentlich von der bei der Retikulosen, wie FRESEN in seiner ausführlichen Arbeit über die Retikulosen darlegt. Während bei der Lipoidgranulomatose die Herde vorwiegend in den Belegknochen des Schädels zu finden sind, zeigt nur ein kleiner Teil der Retikulosen Herde im Skelettsystem und dann auch meistens in anderen Skelettabschnitten.

Nach dem klinischen Verlauf der Retikulose, die in allen beschriebenen Fällen zum Tode führte, dem anatomischen und histologischen Bild handelt es sich bei dieser generalisierten Wucherung des RS um eine maligne Neoplasie, die LETTERER bereits bei seiner ersten Beschreibung des Krankheitsbildes zu den aleukaemischen Leukosen in Parallele setzt. — Wir schliessen uns nach genauer Untersuchung unseres Materials dieser Auffassung von dem Wesen der Retikulose an. Auch bei unserem Material waren die Zeichen einer Heilung nicht nachzuweisen. — Wir unterstreichen abschliessend die Forderung, dass die Retikulose von allen anderen Erkrankungen, die mit einer allgemeinen Reaktion des RS einhergehen, streng abzugrenzen ist.

Zusammenfassung

Es wird über einen $4^1/_2$ Monate alten Säugling berichtet, der die typischen Symptome der Letterer-Siweschen Erkrankung aufwies. Im Vordergrund des klinischen Bildes standen Hauterscheinungen (Faltenpurpura und eine Unzahl am Rumpf lokalisierter, senfkorngrosser Knötchen) sowie ein Lungenbefund, der röntgenologisch an eine Miliartuberkulose erinnerte. Das Kind kam nach kurzer Zeit ad exitum. Die histologische Untersuchung zeigte retikulär-histiocytäre Wucherungen besonders in der Milz, den Mesenterialwurzellymphknoten und der Lunge.

Contribution to the study of the Letterer-Siwe's Disease.

Report of a case of Letterer-Siwe's disease in a $4^1/_2$ months old infant. The dominant symptoms were skin manifestations (purpuric spots in the flexures and abundant minute nodules localized on the trunk) and pulmonary lesions resembling miliary tuberculosis. The infant died after short time of observation. The post-mortem examination showed reticulo-histiocytic proliferations especially in the spleen, mesenteric lymph nodes and the lungs.

Contribution à l'étude de la maladie de Letterer-Siwe.

L'auteur décrit le cas d'un nourrisson âgé de quatre mois et demi, qui présentait les symptomes typiques de maladie de Letterer-Siwe. A l'examen clinique on était surtout frappé par les lésions cutanées (purpura au niveau des plis et une très grande quantité de nodules de la grosseur d'un grain de moutarde localisés sur le tronc) ainsi que par une image radiologique des poumons ressemblant à celle de la tuberculose miliaire. L'enfant est décédé après peu de temps. L'examen histologique a montré des proliférations réticulo-histiocytaires localisées principalement dans la rate, les ganglions lymphatiques du mésentère et les poumons.

Un caso de enfermedad de Letterer-Siwe.

El autor describe un caso de enfermedad de Letterer-Siwe en un lactante de 4½ meses de edad. Los síntomas dominantes fueron: manifestaciones cutáneas (manchas purpúricas en las regiones de flexión y numerosos pequeños nódulos localizados en el tronco) y lesiones pulmonares semejantes a la forma miliar de la tuberculosis. El lactante falleció desupués de un corto período de observación. El examen post-mortem mostró proliferaciones retículo-histiocitarias, especialmente en el bazo, ganglios linfáticos mesentéricos y pulmones.

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From the Pediatric Department, The Rigshospital, Copenhagen
(Chief: Professor P. PLUM, M.D.)

On Creatinuria in Precocious Puberty

by I. PERSSON

Introduction

The purpose of this work is to investigate creatine and creatinine metabolism in precocious puberty.

Creatinuria is found in children even under normal conditions. It is, however, not a constant phenomenon. Thus KRAUSE and ROSE have found that creatinuria does not occur in some children. In their early investigations FOLIN (1905) and KLERCKER found that normal adults excrete creatinine in the urine in relatively large amounts, but little or no creatine; creatine is found especially in women. Also ROSE, ELLIS & HELMING found that women, after oral administration of creatine, excrete more of this substance than men.

In accordance with the fact that a change in creatinuria occurs in the sexually mature individual, it has been shown that it is possible to diminish the spontaneous creatinuria of children by means of giving male or female sex hormones (GENTILI). LIGHT & WARREN, and WANG, GENTHER & HOGDEN have, in their investigations, established that creatinuria is found in normal puberty in some individuals, but is absent in others. On the other hand it is not apparent from their investigations whether variation in the creatine excretion from day to day occurs in any one case.

The effect of creatine administration in two cases of precocious puberty has been observed by BEUMER & FASOLD. In one boy with macrosomia praecox, but with infantile testes, they found that intravenous creatine was excreted unchanged. In an 8 year old girl, who had begun to menstruate, and had fully developed sex organs, it was found, on the other hand, that intravenous creatine was completely broken down.

Methods

The investigations cover five children with precocious puberty. The case histories will be outlined below.

During the period of investigation the children were on a meat-free and fish-free diet. The quantity of creatine and of creatinine in the urine was estimated according

to FOLIN's method (1914). Moreover, according to AXEL THOMSEN, the "creatine index" has been defined as: $\frac{\text{total creatinine} \times 100}{\text{performed creatinine}}$. When this technique is used a creatine index of 95–105 means that the urine is free from creatine.

Case Histories

Case 1.

A girl aged $6^3/_4$, the fourth of five children. The mother and the patient's older sister were about 10 years old when the menarche occurred. The patient's breasts began to develop rapidly at the age of two, and pubic hair began to grow. The menarche occurred one year ago, and menstruation has since occurred with 28–35 days interval and with a duration of from 1–3 days. The bleeding is only slight. Psychologically she corresponded to a child at puberty. Cerebral incidents had never been observed. Her figure was feminine. She was 141 cm in height and weighed 37.8 kg. Her voice was a little deeper than normal. There was relatively dense growth of axillary hair and dense growth of pubic hair of feminine distribution. The breasts were fairly well developed with plenty of glandular tissue. The labia and the circumanal region were pigmented. There was no hypertrophy of the clitoris.

X-ray examination of the scull showed no abnormality. The epiphyseal lines were small as at the age of 12–14 years. The blood pressure was 105/40. The hormone analysis corresponded to that found during puberty. Gynaecological examination showed that the uterus was slightly hypoplastic (but of course much larger than should correspond to the child's age). The ovaries were normal. Endometrial biopsy showed the endometrium to be in the proliferative phase.

Table of the creatine index for 7 consecutive days in patient no. 1.

Day	1st	2nd	3rd	4th	5th	6th	7th
Creatinine (in mg) . . .	476	511	583	619	379	459	531
Creatine (in mg)	38	0	41	0	0	0	26
Creatine index	107	100	106	100	100	100	104

Case 2.

A girl aged 8 years, 9 months, the fourth of 4 children. The patient is a twin. No similar cases are in the family. Nearly 3 years ago she fell down some stairs and sustained a fractured skull. She was admitted to the hospital, and air encephalography taken some months later showed slight dilatation of the left lateral ventricle. There have been no cerebral incidents since then. Two years ago the patient began to grow rapidly. During the last three months there has been growth of axillary hair, and in the last month of the pubes also. The menarche has not occurred.

The figure was infantile, although the hips were rather wide. She was 137 cm in height and weighed 31.3 kg. The voice was normal. Neurological examination showed nothing abnormal. There was fairly well developed growth of dark axillary hair. There was a little pubic hair, mostly light coloured. There was no breast development. The clitoris was not enlarged.

X-ray examination of the skull and epiphyseal lines showed nothing abnormal. Air encephalography showed slight dilatation of the left lateral ventricle posterially, and a restricted collection of air was seen over the right occipital lobe, which suggested a local atrophic brain condition. The blood pressure was 105/45. The result of hormone analysis was that no gonadotropin or oestrogen hormones could be demonstrated. The excretion of corticoids was normal, whereas the excretion of 17-ketosteroids was at the upper limit of normal. Gynaecological examination showed the presence of a mobile structure, the size of a hazel nut, in the normal situation for the uterus. The ovaries could not be palpated.

Table of the creatine index for 7 consecutive days in patient no. 2.

Day	1st	2nd	3rd	4th	5th	6th	7th
Creatinine (in mg) . . .	490	1550	859	735	1461	973	897
Creatine (in mg)	81	108	80	60	220	124	91
Creatine index	114	106	108	107	113	111	109

Case 3.

A girl, aged 6 years, 2 months, the fourth of 4 children. There was no familial tendency to precocious puberty. During the last year she had gradually gained in weight, and development of the breasts and of the external genitalia occurred. The menarche occurred 6 weeks prior to admission. The bleeding had been quite heavy. There had never been a cerebral incident.

There was adiposity of typical feminine distribution. She was 115 cm in height, and weighed 25.0 kg. The voice was normal. Neurological examination showed nothing abnormal. There was no axillary hair. The growth of pubic hair was quite marked. The breasts were well developed, with unmistakable glandular tissue. The clitoris was quite small.

X-ray examination of the skull showed nothing abnormal. The blood pressure was 110/80. Hormone analysis did not show gonadotropin, but oestrogens were present as in a sexually mature woman. The excretion of corticoids and 17-ketosteroids was not abnormal. Gynaecological examination showed that the uterus was the size of that of a 12 year old girl. The ovaries were not enlarged. Biopsy showed corpus endometrium in the proliferative phase.

Table of the creatine index for 7 consecutive days in patient no. 3.

Day	1st	2nd	3rd	4th	5th	6th	7th
Creatinine (in mg) . . .	515	420	489	609	327	538	652
Creatine (in mg)	124	0	92	79	15	114	67
Creatine index	121	100	116	111	104	118	109

Case 4.

A boy aged 7 years, 3 months, the first of 2 children. There were no cases of early sexual maturity in the family. He had had pyloric stenosis in infancy. He was said to have always been tall for his age. In the last 6 months the boy's genitalia had grown in size, and at the same time he had gained 10 kg in weight. Growth of pubic hair had begun in the last 3 months. There had been frequent erections, but masturbation had not been noticed. No cerebral incidents had been observed.

He was a large, obese boy. The fat tissue was fairly evenly distributed, although mostly round the loins, the nates, and the lower limbs. He was 135 cm in height and weighed 40.7 kg. His face was rather flushed, and the skin of the nates and lower limbs was mottled. There was no beard, and only single, light-coloured axillary hairs. There was a strong growth of dark pubic and circumanal hair. The penis was 6.5 cm long and 6 cm in circumference. The skin of the penis and scrotum was pigmented, and the scrotal skin was wrinkled. The testes measured 2 × 4 cm and were of firm consistency. The prostate was small and could hardly be felt. Neurological examination showed nothing abnormal apart from brisk and equal knee jerks over a slightly increased zone.

X-ray examination of the urinary tract showed nothing abnormal. On the other hand, the skull was shown to be very large, with marked digital impressions; the sutures were normal. The sella was very flat. The epiphyseal lines corresponded more or less to the age. Examination of the eyes showed optic atrophy and hemiamblyopia bitemporalis. Electroencephalography showed nothing abnormal. The excretion of hormones was normal with regards to the content of gonadotropin, androgens, and corticoids. On the other hand, the oestrogen content was slightly raised (about 20 mouse units per day), and the content of neutral 17-ketosteroids was likewise slightly raised (up to 5.1 mg per day). The toxoplasmosis reactions were positive: neutralization reaction (1:1250) and complement fixation reaction (1:16)).

As he had increasing optic atrophy, operation was performed. At operation, a large inoperable retrochiasmal tumour was found, and microscopy showed that it was in all probability an oligodendrocytoma.

Table of the creatine index for 7 consecutive days in patient no. 4.

Day	1st	2nd	3rd	4th	5th	6th	7th
Creatinine (in mg) . . .	588	521	642	538	642	507	439
Creatine (in mg)	89	60	268	67	203	123	81
Creatine index	113	110	136	111	127	121	116

Case 5.

A boy, aged 8 years, 3 months, the second of 3 children. There were no other cases of abnormally early sexual development in the family. At the age of two the parents had noticed that his penis was rather large, and that after that it continued to increase in size. Also, growth of pubic hair occurred, but no axillary hair or beard. Moreover, he grew very tall for his age. At the age of 3 he was admitted to hospital where exploratory laparotomy was performed. This showed bilateral hyperplasia of

the adrenals, but no tumours. Resection was not carried out. The patient was discharged, and in the following years development continued. Masturbation was never noticed, and erections were rare. There had never been a cerebral incident.

He was powerfully built, with well-developed muscles. He was 146 cm in height, and weighed 42.3 kg. The skin was strongly sunburnt. There was scanty beard. Growth of hair in the axillae was marked, and the same on the pubes. There was likewise relatively marked circumanal growth of hair. The penis was 10.5 cm long and 10.0 cm in circumference. The skin of the penis and scrotum was pigmented, and the scrotal skin was wrinkled. The testes measured 2 × 3 cm and were of firm consistency. The prostate was about the size of a walnut and of normal consistency. Neurological examination showed normal findings.

X-ray examination of the skull showed nothing abnormal. Intravenous urography showed nothing abnormal on the right side, but on the left side a mitre-like growth, corresponding to the adrenal, was thought to have been seen, and to be larger than normal; however, no calcification was seen. Hormone analysis showed a markedly elevated excretion of neutral 17-ketosteroids, up to 38.0 mg in 24 hours. Gonadotropin was not demonstrated. The excretion of oestrogen hormones was somewhat increased (between 100 and 200 mouse units per day). The excretion of androgen hormones was as for an adult man (63 international units per day).

Table of the creatine index for 7 consecutive days in patient no. 5.

Day	1st	2nd	3rd	4th	5th	6th	7th
Creatinine (in mg) . . .	792	650	596	739	823	687	874
Creatine (in mg)	114	182	104	162	202	103	181
Creatine index	112	124	115	119	121	113	118

Discussion

These investigations are considered to indicate that creatinuria is not found in some individuals showing precocious puberty, while others have a slightly raised creatine index. These conditions are similar to those found in normal puberty (Light & Warren, Wang, Genther & Hogden).

The changes in creatine-creatinine metabolism in precocious puberty, however, give the impression of being rather unstable. Not only are variations from one individual to another found, but in a single individual great variation is found occasionally in the excretion of creatine per 24 hours.

These variations can hardly be attributed to the diet, as that had a constant composition. However, it is possible to reduce the spontaneous creatinuria of children by the administration of male or female hormones (Centili). It is perhaps justifiable to presume that the variations in creatine excretion found in precocious puberty can be attributed to variations in the hormone production.

On the whole these investigations are considered to indicate that in precocious puberty, as in normal puberty, a change in the creatine-creatinine metabolism occurs. In this respect the condition is similar to that found in sexually mature individuals.

Summary

An investigation of the creatine and creatinine metabolism in precocious puberty seems to indicate that the conditions found correspond to those at normal puberty. Variations in creatine excretion are found, not only from one individual to another, but from day to day in an individual child. These variations perhaps can be attributed to the fluctuation in production of sexual hormones in precocious puberty.

La créatinurie dans la puberté précoce

L'étude du métabolisme de la créatine et de la créatinine dans la puberté précoce semble donner des résultats correspondant à ceux trouvés dans la puberté normale. L'auteur a trouvé que l'excrétion de créatine varie non seulement d'un individu à l'autre, mais aussi d'un jour à l'autre chez chaque enfant. On peut peut-être attribuer ces variations à des fluctuations dans la production d'hormones sexuelles dans la puberté précoce.

Kreatinurie bei Pubertas praecox

Eine Untersuchung über den Kreatin- und Kreatininstoffwechsel bei Pubertas praecox scheint darauf hinzudeuten, dass die Befunde denjenigen bei der normalen Pubertät entsprechen. Schwankungen in der Kreatinausscheidung wurden nicht nur von einem Individuum zum andern gefunden, sondern auch, bei ein und demselben Kinde, von Tag zu Tag. Diese Schwankungen können indessen erklärt werden durch die Schwankungen in der Produktion von Sexualhormonen bei der Pubertas praecox.

La creatinuria en la pubertad precoz

Una investigación sobre el metabolismo de la creatina y creatinina en la pubertad precoz parece indicar que las situaciones encontradas corresponden a aquellas de la pubertad normal. Fueron encontradas variaciones en la excreción de creatina no solo de un individuo a otro, sino también de un día a otro en un mismo individuo. Estas variaciones pueden, quizás, ser atribuidas a la fluctuación en la producción de hormonas sexuales en la pubertad precoz.

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Alkali-resistant Haemoglobin in Thalassaemia

by C. CHOREMIS, L. ZANNOS and C. L. DENTAKIS

Investigations of the last few years, in Italy by BIANCO (1), PUTIGNANO *et al.* (2), VECCHIO (3) and others, in America by SINGER *et al.* (4), have demonstrated that an alkali-resistant haemoglobin fraction is regularly found in thalassaemia and sickle cell anaemia. According to SINGER it may also be encountered, in small concentrations, in hereditary spherocytosis and acquired hematologic disorders like leukemia, aplastic anaemia and pernicious anaemia.

As far as our present knowledge goes, this alkali-resistant haemoglobin is apparently identical with foetal haemoglobin and represents a continued production of foetal haemoglobin beyond the age at which it is still normally present (5, 8, 9). This age is the 5th year, according to SINGER's series of 150 normal children aged between a few days and 6 years (4). According to our series of 500 normal children aged between 2 and 7 years—100 children from each age group—small amounts of foetal haemoglobin may be found occasionally up to the 7th year of life (10).

The concentrations of alkali-resistant Hb observed in different patients with sickle cell anaemia fluctuate between 2–24 per cent according to SINGER (6). Similar values have been reported by other authors. Our findings, in a series of 42 Greeks with sickle cell anaemia, are also in agreement with SINGER's (unpublished data). The agreement of results from different authors is to be expected since the concentration of sickle cell anaemia haemoglobin is usually between 76–100 per cent and the alkali-resistant Hb fraction is theoretically approximately equal to total haemoglobin minus sickle cell haemoglobin (7), which does not permit much wider variations than those already reported.

The problem is more complicated in thalassaemia. In the available literature we have found few reports dealing with the subject. Most of them are from Italian authors who were the first to be interested in it (1, 2, 3), but who, however, used a different and less accurate method than the one of SINGER, which is in use to-day (4), measuring the time needed for the

complete denaturation of haemoglobin and not the concentration of the undenatured haemoglobin. Comparison of results is therefore impossible.

Other authors, using the method of SINGER or a similar one, found values fluctuating between 3.5–100 per cent (4, 11, 13, 12, 16).

It appears, therefore, that a wide variation in the percentage of alkali-resistant pigment is to be expected in thalassaemia. However, our experience in the Paediatric Clinic of Athens University, during the past two and a half years, has been somewhat different. The present study has been undertaken with the purpose of providing an answer to three questions:

1. Whether the concentration of foetal Hb in thalassaemia major is so characteristic of the disease that it could be used as a diagnostic criterion. The answer to this question has practical importance for paediatricians and particularly in the Mediterranean countries. We are very often confronted with serious diagnostic problems in differentiating between acquired hypochromic anaemias in infancy, due to iron deficiency or parasites, and thalassaemia, so frequently seen here.

2. Whether there is any correlation between the severity of the disease and the concentration of resistant haemoglobin present.

3. Whether the presence of foetal haemoglobin is to be expected in thalassaemia trait. This is an important question, especially from the practical point of view, since abnormal amounts of foetal Hb beyond the 7th year of life suggest haematologic pathology of a more or less serious nature. As far as we have been able to find out, concentrations of resistant Hb in a relatively large number of individuals with thalassaemia trait, have been reported mostly by Italian workers (1, 2, 15). Most of them found small amounts of resistant pigment in only a small percentage of the parents.

The present study deals with the determination of alkali-resistant haemoglobin concentrations in the blood of 61 children with thalassaemia major and 53 adults with thalassaemia minima.

Material and Method

The children were patients of the Children's Hospital "St. Sophie". We have included in this series 10 children already described in a previous paper by one of us (14). Of the 61 patients, 56 were diagnosed clinically as typical cases of thalassaemia major. The diagnosis was based on the following criteria: (1) Severe anaemia, Hb usually below 7 g %, (2) Marked hepatosplenomegaly, and (3) Typical thalassaemic facies.

The remaining five children were atypical cases which will be discussed further in detail. They were the only atypical cases encountered within the past two and a half years. The 56 typical thalassaemia cases were chosen at random among the many other typical cases examined at the hospital during the same period of two and a half years. The clinical severity of their disease varied. Some of them required frequent transfusions, others were in a fairly good condition despite their low Hb. Many babies

TABLE 1

Concentrations of alkali-resistant haemoglobin in 61 children with thalassaemia major.

No.	Hb	No.	Hb	No.	Hb	No.	Hb	No.	Hb
1	*82*	13	*75*	25	*65*	37	*79*	49	*75*
2	*59*	14	*77*	26	*85*	38	*60*	50	*60*
3	*91*	15	*59*	27	*72*	39	*76*	51	*89*
4	*65*	16	*59*	28	*84*	40	*52*	52	*60*
5	*87*	17	*77*	29	*57*	41	*85*	53	*40*
6	*78*	18	*85*	30	*63*	42	*75*	54	*35*
7	*80*	19	*88*	31	*83*	43	*52*	55	*44*
8	*70*	20	*54*	32	*83*	44	*64*	56	*40*
9	*69*	21	*81*	33	*74*	45	*62*	57	*10*
10	*71*	22	*80*	34	*81*	46	*69*	58	*17*
11	*85*	23	*82*	35	*50*	47	*60*	59	*17*
12	*76*	24	*80*	36	*57*	48	*63*	60	*7.7*
								61	*93*

fulfilled only two of the three criteria of thalassaemia major at the time they were studied, but developed later the typical facies.

Mild forms of thalassaemia are not seen in our Pædiatric Clinic. The explanation for this may be that because of the fact that thalassaemia occurs only in certain areas of Greece located far from Athens, the patients are brought to Athens only when they are more or less severely ill. The mild forms, then, are probably seen in adult clinics.

The 59 adults were parents of the above children. All of them had a hypochromic anaemia as ascertained by haemoglobin and haematocrit determinations and study of their blood morphology. Resistance of red cells to saline solutions was not determined. We have used SINGER's method in all determinations.

Findings

Our findings are reported in Table 1. As can be seen, alkali-resistant haemoglobin concentrations above 50 per cent were found in 52 of the 56 patients (or 92.9 per cent) with typical thalassaemia major. The highest concentration was 91, the lowest 35 per cent.

The last five cases in Table 1 are described separately because they are unusual. Cases 57 and 58, aged 3 and 7 years respectively, were sisters. Their facies were atypical, their liver and spleen were small, but they had a severe anaemia (Hb below 7 g %) and a high serum bilirubin (above 4 mg %). Their bone changes were moderate. Because of their low alkali-resistant haemoglobin concentration they were studied further by Dr. LEHMANN of St. Bartholomew's Hospital, London. It was shown by electrophoretic and solubility studies that their haemoglobin was a mixture of normal and foetal haemoglobin. Given also their typical blood morphology, they were

considered to be thalassaemia major cases. Cases 59 and 60, aged 9 and 7 years respectively, were similar to the sisters described above, but they were not studied further. One of them had a first cousin with thalassaemia. Their blood was typical of thalassaemia major.

Case 61 should be classified rather as mild form of thalassaemia and not included among the atypical cases. He was a 14 years old boy with marked hepatosplenomegaly but only moderate anaemia (Hb 10 g %) serum bilirubin 2.5 mg % and red cell morphology reminding more of the trait than of the disease.

Among the 53 parents of thalassaemia patients, 9 had foetal haemoglobin (16.9 per cent). The concentration fluctuated between 2–5.4 per cent with the exception of the father of case 61 who had 16 per cent foetal Hb. He was a typical case of thalassaemia trait with a negative physical examination, Hb 12.4 g % and 50 hematocrit. His serum bilirubin was normal.

Discussion

The results indicate that concentrations of alkali-resistant haemoglobin above 50 per cent are found, as a rule, in thalassaemia major. Concentrations below 50 per cent are rather unusual, but they do occur and they can be very low, independently of the severity of the disease. The fact that cases of thalassaemia with only 10 per cent foetal haemoglobin do exist, raises the question whether cases might be encountered with no foetal haemoglobin at all. We believe that such a possibility cannot be excluded on the basis of our present knowledge.

Despite the possibility of wide variations in the percentage of alkali-resistant haemoglobin in patients with thalassaemia major this test has proven a very useful diagnostic tool in our clinic. During the second half of the first year, at an age when usually thalassaemia patients show no typical facies at all, values above 35 per cent, which occur in 100 per cent of our typical thalassaemia major cases, are pathognomonic of thalassaemia major.

While we could find no correlation between the severity of the anaemia and the percentage of resistant pigment, we were impressed by the fact that low values were encountered only in atypical cases with a small liver and spleen. We do not wish to imply that there might be a relationship between the size of the spleen and liver and the concentration of foetal pigment, the number of our cases being too small even for speculation.

On the basis of our present knowledge such cases should be included in the thalassaemic group, but, in any event, electrophoretic and solubility studies should be performed before establishing the diagnosis.

Among the 53 parents of the thalassaemia patients, 16.9 per cent showed

the presence of foetal haemoglobin. The highest value was 16 per cent. It appears therefore that in thalassaemia it is not always possible to differentiate the trait from the disease on the basis of the foetal haemoglobin concentration alone, as is the case in sicklaemia.

Summary

The resistance of Hb to alkali was examined with the method of Singer in 61 children with thalassaemia major and 51 parents with thalassaemia trait. The findings show that concentrations of resistant Hb above 50 per cent are encountered as a rule in thalassaemia major, smaller values being rather the exception. The concentrations fluctuated between 7.7–93 per cent. No correlation could be observed between the severity of the anaemia and the percentage of resistant Hb. However, the few patients with concentrations below 20 per cent had a relatively small liver and spleen and atypical facies. Alkali-resistant Hb was also present in 16.9 per cent of the thalassaemia trait individuals.

L'hémoglobine alcali-résistante dans la thalassémie

La résistance de l'hémoglobine aux alcalis a été étudiée chez 61 enfants atteints de thalassémie, forme majeure, et 51 parents atteints de thalassémie, forme mineure. Il ressort des résultats qu'on trouve en général dans la thalassémie, forme majeure, une concentration en Hb-résistante supérieure à 50 %, une concentration plus faible étant plutôt rare. La concentration variait entre 7,7 % et 93 %. Il n'y avait pas de relation entre la gravité de l'anémie et le pourcentage en Hb-résistante. Chez les quelques patients ayant une concentration inférieure à 20 % le foie et la rate étaient cependant relativement petits et le facies atypique. On a noté la présence de l'hémoglobine alcali-résistante chez 16,9 % des personnes atteintes de thalassémie, forme mineure.

Alkaliresistentes Hämoglobin bei der Thalassämie.

Die Resistenz des Hgl. gegenüber Alkalien wurde nach der Methode von Singer untersucht bei 61 Kindern mit Thalassaemia major und bei 51 Familienangehörigen, d.h. recessiven Trägern der Krankheit. Die Befunde ergeben, dass man bei der Thalassaemia major Konzentrationen von resistentem Hgl. von mehr als 50 % als die Regel betrachten kann; niedrigere Konzentrationen bilden eher die Ausnahme. Der Gehalt an resistentem Hgl. schwankt zwischen 7,7 und 93 %. Zwischen der Schwere der Anämie und dem Gehalt an resistentem Hgl. konnte kein Zusammenhang erkannt werden; doch hatten die wenigen Patienten mit einem Hämoglobingehalt unter 20 % eine rel. kleine Leber und Milz und eine atypische Facies. Alkaliresistentes Hgl. konnte ebenfalls nachgewiesen werden bei 16,9 % der recessiven Träger dieser Krankheit.

El hemoglobina álcali resistente en la talasemia

La resistencia de la Hb al álcali fué examinada por el método de Singer en 61 niños con talasemia mayor (Thalassaemia major) y 51 padres con talasemia menor (thalassaemia trait). Los hallazgos muestran que concentraciones de Hb resistente por encima de 50 % son encontradas como regla en la talasemia mayor (thalassaemia major), siendo excepcionales los valores menores. La concentración fluctuó entre 7.7–93 %.

No pudo observarse correlación entre la severidad de la anemia y el porcentaje de hemoglobina resistente. Sin embargo los pocos pacientes con concentraciones debajo de 20 % tenían un hígado y bazo relativamente pequeños y facies atípica. La Hb álcali resistente estuvo también presente en 16.9 % de los individuos con talasemia menor (thalassaemia trait).

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Paper Electrophoresis of Serum Proteins in Cooley's Anaemia and Sickle Cell Anaemia

by JOHN ALLAMANIS

Previous studies in our clinic and elsewhere have shown that a disturbance of serum proteins is to be found frequently in Cooley's anaemia and sickle cell anaemia (1, 2) (flocculation and turbidity tests). As a rule the older the patient or the more severe the disease, the more probable it is to find the tests positive.

The above observation led us to a more detailed study of serum proteins in these anaemias, with the method of paper electrophoresis.

As far as we have been able to find from the available literature, no study of this kind has been published so far, except for a preliminary report, by DELYIANNIS *et al.* (3), in Salonica, who investigated two cases of Cooley's anaemia and reported an increase of the γ-globulin fraction. The present study has been undertaken with the purpose of determining whether there is a typical electrophoretic pattern in the above anaemias, and if so, whether there is any correlation between the disturbance of serum proteins on the one hand and the severity of the anaemia, the age of the patient and the flocculation tests on the other.

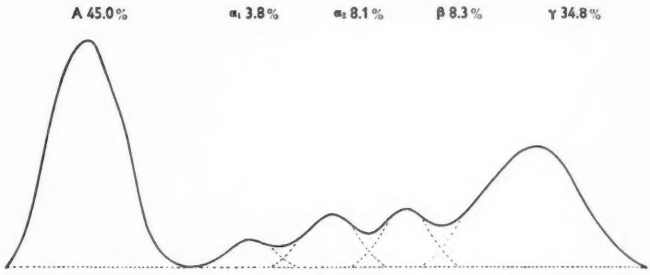
Material and Method

We have studied 48 patients; 36 with Cooley's anaemia, and 12 with sickle cell anaemia. We have classified the Cooley's anaemia patients according to their age into 3 groups.

1) 0–24 months, 11 cases
2) 3– 6 years, 16 „
3) 7–18 „ 9 „

Seven of them had undergone splenectomy 1 month to 3 years previously. In 2 cases, the electrophoretic pattern was determined during an haemolytic crisis.

The sickle cell anaemia cases were children, 6–18 years old. One of them had been splenectomized 2 years previously. In 4 of them, the electrophoretic studies were performed during crisis.



E. B. 3 years old

Typical diagram of Cooley major

Fig. 1.

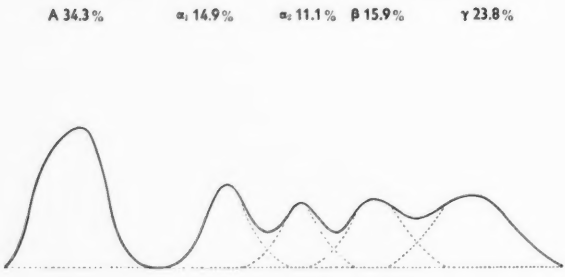
For all determinations we have used the Elphor H electrophoretic instrument of Bender and Hobein, with a veronal buffer of pH = 8.6. The paper strips were stained with a saturated solution of amidoschwartz 10 B in methyl alcohol and acetic acid. We used Whatman No. 1 filter paper.

Results

Cooley's anaemia.—The patients should be divided into 2 categories according to their electrophoretic diagram: the first category includes the infants (11 cases) aged less than 24 months in whom the pattern was almost normal with a slight increase of γ-globulins in all but two cases. In the latter the pattern was similar to the one found in the second category of the older children (that is, it showed a decrease in albumin—average 52 per cent, lowest 42 per cent, an increase in γ-globulins—average 30 per cent, highest 42 per cent, and a slight decrease in α_1, α_2 and β-globulin—average 3, 7.5, and 9.5 per cent respectively). Figure 1 is a representative electrophoretic pattern of serum protein disturbance in the second category. The clinical conditions and the laboratory findings in the above two infants with an abnormal pattern indicated that their disease was more severe than in the other nine.

There was no change in the pattern during haemolytic crisis; neither did splenectomy seem to have caused any alteration of the serum proteins.

Flocculation and turbidity tests were as a rule more positive in the cases with γ-globulin above 30 per cent, independently of the age of the patients. After splenectomy, however, previously positive liver function tests reversed to negative in about 50 per cent of the patients, despite the fact that the γ-globulins were greatly increased in the electrophoretic studies.



K.S. 14 years old

Sickle cell anaemia during crisis

Fig. 2.

No correlation could be found at the time of the examination between the degree of anaemia and the concentration of alkali-resistant haemoglobin on the one hand and the electrophoretic pattern on the other.

Sickle cell anaemia.—No difference was observed between sickle cell anaemia and Cooley's anaemia except for a smaller increase in γ-globulins in the former. However, the two types of anaemia differed markedly during crisis. Figure 2 is a typical diagram of a sickle cell anaemia crisis. The most characteristic finding is an increase above normal of the α_1 and α_2 globulin fractions instead of the usual decrease. The albumin fraction shows a further decrease while the γ-globulins remain increased. The findings were similar in the 4 cases examined during crisis. The pattern showing the greater degree of abnormality was obtained from a patient who died during crisis a fortnight later.

Discussion

Our results indicate that the electrophoretic pattern of serum proteins is approximately the same in Cooley's anaemia and sickle cell anaemia. This pattern is not typical of the above anaemias. Similar findings have been reported by other authors in acquired anaemias (4) and other diseases not affecting the haematopoetic system.

The γ-hyperglobulinaemia encountered in our cases is a sure indication of a pronounced participation of the reticulo-endothelial system in the anaemias in question (5, 6).

The view could be upheld that the electrophorætic changes in such anaemias are secondary, resulting from cirrhotic changes in the liver (7), which

as reported in the literature, occur inevitably if the patients live long enough. However, their occurrence in infants and young children in whom cirrhotic changes are not yet present, and their difference from those of cirrhosis (severe hypoalbuminaemia, great increase of γ-globulins), argue against this theory.

The positiveness of flocculation and turbidity tests runs parallel to the increase in γ-globulins and the decrease in albumin. Their reversal to the negative, after splenectomy, despite the fact that the pattern shows no essential change, indicates a probable qualitative alteration in the molecular composition of the fractions, without a simultaneous physicochemical behaviour, i.e. their electrical charge.

Still, the whole problem of the liver's participation in the pathogenesis of these anaemias, as well as the importance of the positive liver function tests, remains to a large extent unsolved.

Another point meriting attention is the correlation between the electrophoretic diagram and the age of the patient. The changes become more pronounced as the age of the patient increases. In these cases, possibly the occurrence of a secondary cirrhosis should be taken into consideration.

As mentioned previously, the electrophoretic picture of sickle cell anaemia during crisis differs radically from that in Cooley's anaemia. Of course, important differences exist between the clinical picture and the mechanism of the crisis in the two types of anaemia.

The electrophoretic patterns in sickle cell anaemia during crisis greatly resemble those described in the crush syndrome, wounds, burns and, generally, whenever extensive tissue destruction occurs (8). This has also been observed in experiments upon animals with the administration of ACTH. That there can be any correlation between the foregoing and the crisis in sickle cell anaemia, is a point which invites speculation.

The question as to whether the biological changes of the serum proteins precede or follow the clinical manifestation of the crisis, and whether electrophoresis can serve in diagnosing the crisis, remains unanswered at present.

It is well known that the erythrocyte sedimentation rate is closely related to the height of the curve of the α-globulins (9).

It would be possible for the lower rate of sedimentation noted in Cooley's and sickle cell anaemia to be due not only to red cell factors but also to plasma factors, that is, to a reduction in α-globulins.

As regards the query whether the alterations of the pattern are of prognostic significance, we are inclined to the believe that it does, and to this end further observations and investigations will be carried out in the near future.

Summary

The serum proteins of 36 patients with Cooley's major and 12 with sickle cell anaemia were studied by the method of paper electrophoresis. The electrophoretic pattern was almost normal in 9 of 11 infants with Cooley's anaemia aged less than 24 months, while in the remaining two, it was similar to the one observed in the older age group (that is, it showed a decrease in albumin, a slight decrease in α_1, α_2, and β-globulins, and an increase in γ-globulin).

No difference was observed when the pattern was taken during an haemolytic crisis or in splenectomized patients. The electrophoretic studies in the sickle cell anaemia patients showed the same abnormalities except for a lesser increase in γ-globulin. During crisis, a quite different electrophoretic picture was observed. A similar electrophoretic pattern has been described in the crush syndrome.

L'électrophorèse sur papier des protéines sériques dans l'anémie de Cooley et l'anémie à cellules falciformes.

L'auteur a étudié par la méthode de l'électrophorèse sur papier les protéines du sérum chez 36 patients atteints d'anémie de Cooley, forme majeure, et 12 atteints d'anémie à cellules falciformes. Le tracé électrophorétique était normal chez 9 des 11 nourrissons, ayant un âge inférieur à 24 mois et atteints d'anémie de Cooley. Chez les deux autres nourrissons il ressemblait au tracé trouvé chez le groupe d'enfants plus âgés, c.-à-d. qu'il présentait une diminution de l'albumine, une légère baisse des α_1, α_2 et β-globulines et une augmentation de la gamma-globuline. Le tracé n'était pas changé lorsqu'il était étudié pendant une crise hémolytique ni chez des personnes splénectomisées. Chez des patients atteints d'anémie à cellules falciformes le tracé montrait, à l'exception d'une légère augmentation de la gamma-globuline, des altérations identiques; il était cependant très différent pendant une crise. Un tracé électrophorétique semblable a été décrit dans le « crush syndrome ».

Papierelectrophoretische Untersuchungen der Serumproteine bei der Cooley-Anämie und der Sichelzellanämie.

Die Serumproteine von 36 Patienten mit Cooley-Anämie und von 12 Patienten mit Sichelzellanämie wurden untersucht. Bei 9 von den 11 Kindern mit Cooley-Anämie und einem Alter von weniger als 24 Monaten war das electrophoretische Diagramm weitgehend normal. Bei der restlichen 2 glich es eher demjenigen in der höheren Altersgruppe, d. h. es zeigte: Verminderung des Albumins, leichte Abnahme des α_1, α_2 und β-Globulins und Vermehrung des Gamma-Globulins. Es bestand kein Unterschied zwischen den Diagrammen, die während einer hämolytischen Krise oder bei splenectomierten Patienten gefunden wurden. Das electrophoretische Diagramm bei den Patienten mit Sichelzellanämie zeigte die gleichen Anomalien, doch war die Vermehrung des Gamma-Globulins weniger ausgeprägt. Während einer Krise veränderte sich hier das electrophoretische Bild vollkommen. Diese electrophoretischen Befunde gleichen denjenigen beim Crush-Syndrom.

Estudio de las sero-proteinas con el método del papel electroforético en anemia de Cooley y en anemia a células falciformes.

Las sero-proteinas de 36 pacientes con anemia de Cooley y 12 con anemia a células falciformes fueron estudiadas con el método del papel electroforético. El di-

grama electroforético fué casi normal en 9 de 11 niños con anemia de Cooley de edad inferior a 24 meses, mientras en los dos restantes fué similar al observado en el grupo de más edad, esto es: una disminución de la albúmina, una ligera disminución en las globulinas α_1, α_2 y β y un aumento en la gamma-globulina. No fué observada diferencia cuando el diagrama fué obtenido durante una crisis hemolítica o en pacientes esplenectomizados. Los diagramas electroforéticos en pacientes con anemia a células falciformes mostró las mismas anormalidades, excepto un más discreto aumento en la gamma-globulina. Durante las crisis, se observó un cuadro electroforético completamente diferente. Un diagrama electroforético similar ha sido descrito en el «crush syndrome».

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From the Children's Clinic, Helsinki, Finland

Hemolysis of Human Blood Caused by Oxygen and Its Prevention with Vitaman E

Preliminary Report

by NIELS RÄIHÄ

In cases of asphyxia in newborn and premature infants the oxygen incubator is used in general treatment. Retrolental fibroplasia occurs more often in infants treated in oxygen incubators than in normal atmosphere. In a lecture by BAKKER given at the Children's Hospital in Helsinki he suggested that an increased oxygen concentration in the blood of newborn children might cause hemolysis. The reason for this thought was the increased frequency of kernicterus in babies treated with oxygen. GORDON has shown that the hemolysis caused *in vitro* by the addition of H_2O_2 can be prevented if the blood donor is given vitamin E before the blood sample is taken.

The above-mentioned observations have been the stimulus for our investigations.

Materials, Methods and Results

Blood samples of 50 ml were taken from normal adults. The coagulation was prevented by 0.5 ml heparin solution. From this blood, 3 ml samples were measured into sterile bottles of equal volume. After the administration of blood the bottles were carefully filled with pure oxygen, closed and incubated in temperatures of 4° C, 20° C and 37° C. The degree of hemolysis was tested using a Beckman spectrophotometer operating at 545 mμ. Before the analysis the blood samples were centrifuged and 0.2 ml plasma was mixed with 3 ml 0.1 % Na_2CO_3 solution or 0.9 % NaCl solution. The hemolysis was tested in successive bottles after an incubation period of 1, 2, 4, 6 and 24 hours. The results can be seen in Fig. 1.

In the same manner the hemolysis at different oxygen concentrations after a 24-hour incubation at 37° C was tested.

The tests were repeated again after an intake (oral) of 100 mg of vitamin E, given 24 hours before the collection of blood samples. The results of these tests can be seen in Fig. 2.

In some cases the hemolysis after 24 hours was not as marked as in the above cases, and further studies with a simultaneous vitamin E determination is needed.

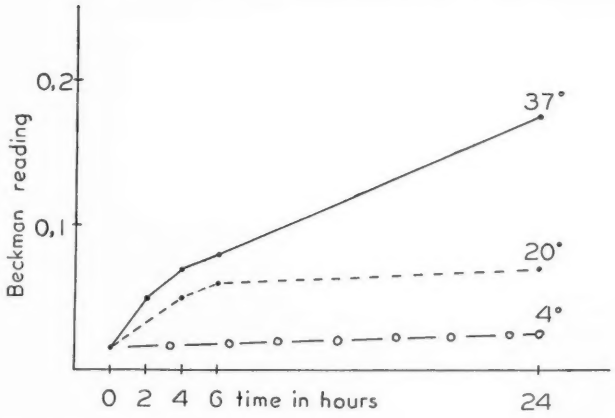

Fig. 1. Degree of hemolysis at different temperatures and increasing time in 100 % oxygen.

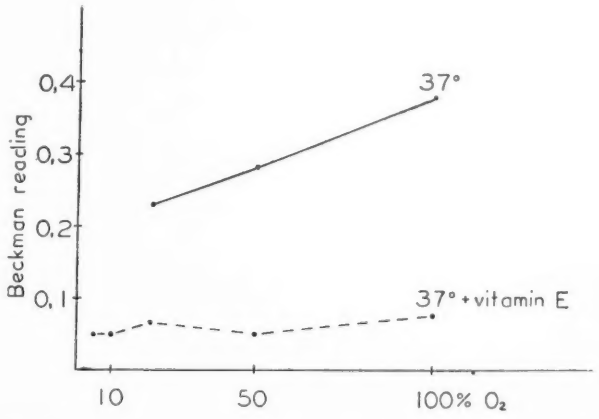

Fig. 2. Degree of hemolysis at 5 %, 10 %, 20 %, 50 % and 100 % oxygen after a 24-hour incubation at 37° C, before and after an intake of 100 mg of vitamin E.

The hemolysis of umbilical blood was then tested as above. Vitamin E was administered to the mothers the day before delivery. From the experimental results it seemed that the change in oxygen concentration has no relationship to the hemolysis of blood from the umbilical cord. In general the hemolysis of the umbilical blood was marked even at low oxygen concentrations, and with increasing oxygen concentration the degree of hemolysis was fairly constant. It was, however, noted that the degree of hemolysis of umbilical blood was directly proportional to the incubation time.

Discussion

From these experiments it is evident that the degree of hemolysis in some cases is directly proportional to the oxygen concentration (*in vitro*). It is also evident that vitamin E given the day before the test has an inhibitory effect on the hemolysis. If the oxygen effect *in vivo* is the same, it is possible that the breakdown of erythrocytes and the production of bilirubin is increased with an increased oxygen tension in the blood. The experiments also point out that the vitamin E administration might increase the viability of the erythrocytes in blood and is possibly useful in cases where blood is oxygenated outside the organism. The results obtained from the experiments with umbilical blood indicate that there are marked differences between the fetal and adult erythrocytes.

Summary

1. Hemolysis tests were performed on blood incubated with increasing oxygen concentrations.

2. It was concluded that the degree of hemolysis in some cases is directly proportional to the concentration of oxygen.

3. Vitamin E administered to the tested subjects has an inhibitory effect on this hemolysis.

4. It seems that fetal blood, due to some physiological effect, has a different behaviour under the above conditions.

Acknowledgement.—This paper owes much to the technical assistance of Mrs. K. LAINE.

Hémolyse du sang humain par l'oxygène et l'effet préventif de la vitamine E.

Des tests d'hémolyse ont été faits sur du sang ayant subi l'incubation avec des doses croissantes d'oxygène. On a pu tirer la conclusion que dans certains cas le degré d'hémolyse est directement proportionnel à la concentration d'oxygène. La vitamine E administrée aux sujets examinés a un effet inhibiteur sur cette hémolyse. Il semble que le sang du fœtus, à cause d'un certain effet physiologique, se comporte différemment dans les circonstances mentionnées plus haut.

Die durch Sauerstoff verursachte Hämolyse des menschlichen Blutes und ihre Verhinderung durch Vitamin E.

Es wurden Hämolyseuntersuchungen mit in steigenden Sauerstoffkonzentrationen inkubiertem Blut durchgeführt. Man stellte fest, dass der Grad der Hämolyse in einigen Fällen direkt proportional der Sauerstoffkonzentration ist. Gibt man den Versuchspersonen Vitamin E, so hat dieses einen hemmenden Effekt auf die Hämolyse. Auf Grund gewisser physiologischer Wirkungen scheint sich das Fötalblut unter den obengenannten Bedingungen anders zu verhalten.

Hemólisis de sangre humana con oxígeno y efecto inhibitorio de la vitamina E.

Se realizaron pruebas de hemólisis con sangre incubada con concentraciones crecientes de oxígeno. Conclúyese que el grado de hemólisis en algunos casos es directamente proporcional a la concentración de oxígeno. La vitamina E administrada a los sujetos sometidos a la prueba tuvo un efecto inhibitorio sobre la hemólisis. Parece que la sangre fetal, debido a algún efecto fisiólogico, tiene un comportamiento diferente en las condiciones citadas.

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Aus der Univ.-Kinderklinik Rostock (Direktor: Professor Dr. med. F. THOENES)

Das Vorkommen von Colitypen der Gruppe 0 26 bei Säuglingsdurchfällen

von H. W. OCKLITZ *und* E. F. SCHMIDT

„Eine zahlenmässig grosse, ins Gewicht fallende Rolle spielen die Coli der 0-Gruppe 26 in unserem Material nicht" — das konnten wir noch in unserer letzten umfassenden Arbeit (19) über die Bedeutung säuglingspathogener Colistämme schreiben, der Escherichiatypen, die wir nach der Erstbezeichnung durch ADAM (Literaturangaben s. 1) im folgenden Dyspepsiecoli (DC) nennen. Dieser Arbeit lag unser gesamtes DC Krankengut bis August 1952 zugrunde. Indessen hat sich das Bild völlig gewandelt. Unter den DC — über die Problematik des Begriffes gerade hier wird noch zu reden sein — finden wir jetzt die Coli der Gruppe 0 26 am meisten. Diese auffallende Häufung und manches dabei beobachtete Detail scheinen uns gerade im Hinblick auf die Wertung der Coli 0 26 innerhalb der DC-Gruppe wichtig und mitteilenswert.

Angeregt durch die ersten Mitteilungen über Säuglings-Enteritiden, bei denen DC der 0-Gruppe 55 gefunden worden waren, fahndete ØRSKOV nach Colitypen der Gruppen 0 26 und 0 44. BIERING-SORENSEN, KNIPSCHILDT, v. MAGNUS und TULINIUS (3) nämlich hatten — bei Untersuchungen zur Klärung von schweren Hospitalinfektionen auf Kopenhagener Säuglingsstationen — im Jahre 1943/44 eine Reihe von Colibakterien isoliert, von denen KNIPSCHILDT feststellte, dass sich öfter neben den Colibakterien der Gruppe 0 44 solche der Gruppe 0 26 fanden. Aus 50 Stuhluntersuchungen kultivierte er 8mal Coli 0 26 (und 7mal 0 44).

1951 konnte ØRSKOV von seinen ausführlichen Untersuchungen über die Coli 0 26 berichten (20). Es handelte sich um insgesamt 62 Stämme, meistens aus Dänemark, einige auch aus England und Finnland. ØRSKOV beschreibt in dieser seiner ersten Arbeit hauptsächlich die bakteriologische Differenzierung, u. a. auch die biochemische Einteilung in 3 Typen und erwähnt überdies das Vorkommen von Coli 0 26 bei Kälberruhrfällen. Auf die Klinik der Säuglingserkrankungen wird von ihm nicht näher eingegangen. Das von ØRSKOV herausgestellte Vorkommen von Coli der Gruppe 0 26 bei Säuglingsdurchfällen wurde von anderen Autoren ebenfalls gefunden, resp. bestätigt.

Sieht man diese Arbeiten durch, so fällt, von einigen noch zu erwähnenden Ausnahmen abgesehen, auf, dass ziemlich allgemein, ebenso wie in unserem früheren Krankengut (s. 19), *der zahlenmässige Anteil der Coli 0 26 innerhalb der ganzen DC-Gruppe nur gering war.*

So fanden BRAUN und RESEMANN (6) den Coli 0 26 in einem $1^1/_2$ jähr. Untersuchungsabschnitt bei 9 Säuglingen, wovon 8 Kinder eine z. T. schwere Dyspepsie hatten. Wir selbst (18) berichteten in unserer ersten Mitteilung über nur einen Fall, in unserer letzten zusammenfassenden Arbeit (19) über insgesamt 22 Kinder mit einem Coli 0 26-Befund. Weiter wurden diese Coli-Stämme von MARGET (16) 3mal, von HOSTER und KRÜGER (10) 19mal isoliert. Auch KUNDRATITZ und GROSS (14) fanden Coli 0 26 19mal in Wien, woher auch KREPLER und ZISCHKA (13) über sporadisches Vorkommen berichten. BERGER (2) schreibt über 16 Fälle aus dem Kinderspital Basel. LE MINOR und Mitarbeiter (15) teilen ihre Untersuchungen über 13 in Paris und 4 in Nordfrankreich gefundene Stämme mit. Und VINZENT und Mitarbeiter (26) fanden in Le Havre 6 Fälle unter 264 Säuglingen.

Drei Arbeiten in dieser Reihe nehmen dabei nun eine gewisse Sonderstellung ein. Einmal ist es die Arbeit von RANTASALO und HALLMANN (21), die aus Finnland (Helsinki) über ihr DC-Krankengut berichten und feststellen, dass die Coli der 0-Gruppe 26 29mal vertreten sind und *damit an der Spitze sämtlicher säuglingspathogener Coli* in ihrem Material stehen. Dieser 1953 erschienenen Arbeit folgt 1954, ebenfalls aus Finnland, die Arbeit von GRÖNROOS (9), der das Material aus Turku untersuchte. Bei 865 Dyspepsien, sämtlich Kindern unter 2 Jahren, fand er 58mal Coli der Gruppe 0 26. Es wird hier also zum ersten Male über eine wesentlich grössere Zahl berichtet, als in den oben angegebenen Mitteilungen.

Und schliesslich ist hier noch besonders die Arbeit von SCHIAVINI und ANDREONI (22) zu erwähnen, allerdings nicht aus Gründen der grossen Zahl. Sie berichten über 10 Fälle, bei denen DC 0 26 gefunden wurden — interessant ist aber ihre Tabelle der *Verteilung dieser Befunde* über die letzten Jahre. Es zeigt sich nämlich, dass die Coli 0 26 im Jahre 1953 gehäuft gefunden wurden, dagegen vorher überhaupt nicht und dass andererseits die bis dato isolierten DC 0 111 und 0 55 im Jahre 1953 verschwunden sind.

Zusammenfassend lässt sich über die Coligruppe 0 26, von denen bisher nur die Varianten 0 26 : B 6 : H 11 und 0 26 : B 6 : – (20) gefunden wurden, also folgendes sagen. Es handelt sich bei ihnen um Keime, die einmal keineswegs ubiquitär sind, die andererseits bei Säuglingsdurchfällen gefunden wurden, und zwar nicht bei Epidemien, sondern bei sporadischen Fällen. Das wird durch die Tatsache unterstrichen, dass in den meisten Mitteilungen die Aufnahmefälle weit über die in der Klinik übertragenen dominieren (2, 6, 10, 26). Weiter wurden diese Keime bei Erwachsenen isoliert (17), sowie, wie erwähnt, aus Kälberruhrstühlen (20) und bei boviner Mastitis (8).

Wie steht es nun mit der Anerkennung der Coli 0 26 als säuglingspathogene Keime, als DC?

In allerdings längere Zeit zurückliegenden Arbeiten kamen BRAUN und RESSMANN (6) vor allem auf Grund der Tatsache, dass sie keine Übertragung dieser Coli in der Klinik beobachten und auch ihr negatives Verhalten im Erwachsenenversuch konstatieren konnten, zu der Auffassung, dass die Beurteilung dieser Coli noch mit grosser Zurückhaltung erfolgen sollte. Offenbar unter dem Eindruck des ihm geglückten Nachweises spezifischer Agglutinine in Säuglingsseren (7) bezieht aber doch wohl heute auch BRAUN die Coli 0 26 in die DC-Gruppe ein, ohne auf das Argument des fehlenden Kontagionsvermögens an dieser Stelle (7) näher einzugehen. Auch BERGER (2) scheint das Argument des fehlenden Kontagionsvermögens angreifbar. Er hält die Coli 0 26 für krankmachend, wenngleich für weniger contagiös als die übrigen DC. KUNDRATITZ und GROSS (14) betonen ebenfalls die geringere Infektiosität der Coli 0 26, halten sie aber für pathogen, wenngleich nicht in so starkem Grade wie die DC 0 111 — ein Standpunkt, der in gleicher Weise von RANTASALO und HALLMANN (21) vertreten wird.

Ehe wir selbst zur Wertung der Coli 0 26 innerhalb der DC-Gruppe Stellung nehmen, seien zunächst unser *klinisches Krankengut* und anschliessend die Beobachtung einer *Kleinraumepidemie* mitgeteilt.

Wir können über 31 Fälle des ganzen Jahres 1952 berichten, wovon ein Teil schon in unserer letzten Arbeit erwähnt wurde (19), über 62 des Jahres 1953 und über 65 in den Monaten Januar bis Juli 1954. Diese Zahlen zeigen die *ständige Zunahme* gerade *der Coli 0 26* in unserem Krankengut, wobei noch erwähnt werden muss, dass wir demgegenüber kaum DC 0 55 und 0 25, überhaupt nicht 0 86 und auch seltener 0 111 beobachtet haben. Über eine Häufung der Coli 0 26 im vorigen Jahr berichten, wie schon erwähnt, auch SCHIAVINI und ANDREONI (22) aus Novara.

In diesem Zusammenhang darf gleich auf *die jahreszeitliche Verteilung* unserer Fälle eingegangen werden. Sie wird in Abb. 1 dargestellt. Es zeigt sich, besonders, wenn man die Fälle des 1. Halbjahres 1954 mit einbezieht, dass keine Bevorzugung einer Jahreszeit, mindestens keine Bevorzugung der Winter- und Frühjahrsmonate zu erkennen ist. Das gilt, wie die Abb. zeigt, sowohl für die Klinik- wie für die Aufnahmefälle. Es ist ja in einer Reihe von Arbeiten auf die besondere Häufung gerade aller DC-bedingten Durchfallserkrankungen in den Wintermonaten hingewiesen worden (Literaturangaben s. 19). Andere Autoren und wir selbst auch haben eine gleichmässige Verteilung aller DC-Fälle über das ganze Jahr feststellen können (16, 18, 19, 21, 25) oder die geringste Häufung im Winter (24), resp. sogar die stärkste im Sommer ((9): 40,6 % aller Fälle).

Es kann also u. E., um das hier schon vorweg zu nehmen, das Fehlen des Wintergipfels nicht etwa als Argument gerade gegen die Pathogenität der Coli 0 26 verwertet werden.

Von unseren 158 Fällen, bei denen Coli 0 26 gefunden wurden, traten *52 Fälle in der Klinik* auf und *106 waren Aufnahmen*. Es ist also auch in unserem Krankengut so, dass die Coli 0 26 weitaus weniger als die übrigen

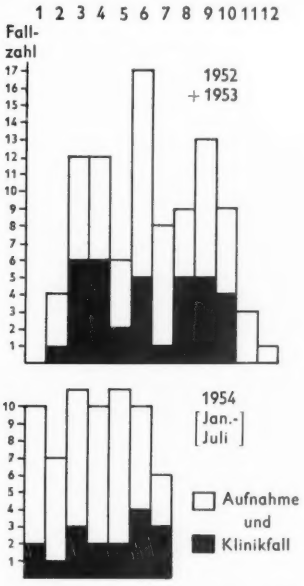

Abb. 1. Jahreszeitliche Verteilung der Coli O 26-Befunde (s. Text).

DC (s. dazu 19) innerhalb der Klinik zu Übertragungen führten. Vorgekommen sind sie jedoch, und zwar in einem nicht ganz geringen Prozentsatz (32,9 %). Wir haben hier, eben um die Übertragung in unserem eigenen Hause herauszustellen, die Fälle zu den Aufnahmen zugeschlagen, die sensu strictiori ebenfalls Klinikfälle sind, nämlich aus Heimen und anderen Krankenhäusern stammen. Eine wesentliche Verminderung der Aufnahmen, von denen man selbstverständlich im Einzelfall auch nicht mit Sicherheit den Kontakt mit anderen Säuglingen ausschliessen kann, ergibt sich jedoch durch ihre Zahl nicht — es handelt sich im gesamten Krankengut um nur 12 Säuglinge (darunter 5 neugeborene Frühgeburten).

Die Häufigkeit der Klinikfälle in den einzelnen Jahren variierte zwar — es waren 1952 rund 32 %, 1953 40 % und 1954 rund 26 % — diese Differenzen liegen jedoch noch innerhalb des statistischen Zufallsbereichs, so dass man eine Schlussfolgerung, etwa bezüglich der Pflegequalität, nicht ziehen darf.

Betrachten wir die *Relation der enteral* (e.) und *der parenteral* (p.) *bedingten* Fälle, so ist hier zunächst noch mehr als in einem Krankengut, das sowohl unspezifische wie DC-Dyspepsien birgt, auf die Problematik dieses Begriffes hinzuweisen. Wir haben hier, wie auch in unserer letzten

Arbeit (19), alle diejenigen Fälle zu den parenteral ausgelösten gezählt, bei denen sich neben der spezifischen Durchfallsstörung eine Herd- oder Allgemeinerkrankung fand, die erfahrungsgemäss eine Dyspepsie auslösen *kann*. Es handelte sich grösstenteils um grippale Infekte bis zu Bronchitiden, kaum Pneumonien, um Otitiden oder, in einem Falle, eine Dermatose. Dass de facto diesen Erkrankungen *generell* die pathogenetische Praevalenz vor der DC-Infektion zukommt, ist nicht anzunehmen. Andererseits können wir doch den Standpunkt von KNOPF (12) — der sich in einer sehr interessanten Studie u. a. mit der Frage beschäftigt, wieviele parenterale Infektionen überhaupt zur Dyspepsie führen und hier zu erstaunlich kleinen Zahlen kommt — nicht teilen: Für KNOPF ist der DC-negative Stuhlbefund eine wesentliche Voraussetzung der Diagnose „parenteral-bedingte Dyspepsie", wenngleich er an anderer Stelle auch p. ausgelöste DC-Enteritiden konzediert. Und auf diesen Punkt kommt es, wie wir schon in unserer Monographie ausgeführt haben (19), u. E. sehr wesentlich an.

Bei den e. bedingten spezifischen Dyspepsien nämlich dürfte das ausschlaggebende krankheitsformende Moment in den DC zu suchen sein, beim Gros der p. bedingten Dyspepsien in der Herd- oder Allgemeinerkrankung, während es sich u. E. gerade bei der Untergruppe der p. ausgelösten Dyspepsien *mit DC-Befund* im Einzelfalle sehr schwer sagen lässt, ob die DC nur als „Gelegenheitsarbeiter" (19) während der p. Erkrankung die Durchfallsstörung unterhalten, ebenso wie es andre Erreger und vielleicht auch Normalcoli tun könnten, oder die Dyspepsie, p. angestossen, autonom weiterläuft. Da also bei den e. Dyspepsien die DC weitgehend allein das Krankheitsbild formen dürften, bei den p. spezifischen Dyspepsien ihre Funktion jedoch, wenn schon in wechselnder Intensität, mit der p. Krankheitskomponente konkurrieren mag, ist u. E. eine Abtrennung und gesonderte Behandlung dieser Fälle berechtigt.

Wie ein Blick auf die Abb. 2 zeigt, ist das Überwiegen der rein enteralen Fälle über die parenteralen offensichtlich. Lässt man die Keimträger aus dem Spiel, so stellt sich das Verhältnis der e. zu den p. Durchfallserkrankungen wie 111:34, dh. rund 3:1. Es sind also, und das erscheint uns gerade im Zusammenhang mit dem vorher Gesagten wichtig, die Fälle, bei denen neben den Coli 0 26 kein anderes schwereres pathogenetisches Moment zu finden war, weitaus in der Überzahl.

In Bezug auf *das Alter* ist auch hier wieder die gleiche Feststellung zu treffen, wie wir sie früher bei der Auswertung des DC-Krankengutes machen konnten (19), dass sich nämlich die p. Fälle ziemlich gleichmässig über das ganze 1. Lebensjahr verteilen, während die e. Durchfallserkrankungen massiert in den ersten Lebensmonaten zu finden sind (Abb. 2). D-

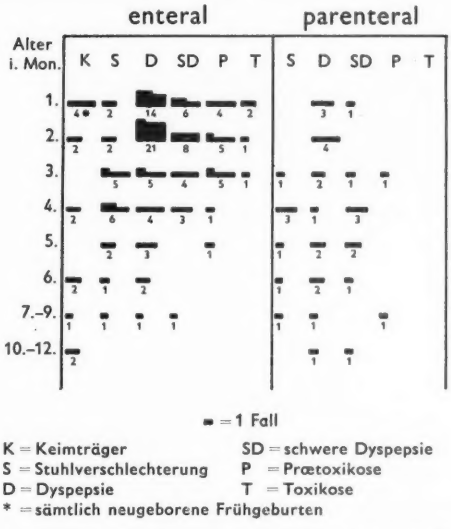

Abb. 2. Verteilung der enteral und parenteral bedingten Coli 0 26-Fälle auf Schweregrad der Erkrankung und Alter.

rechnet man z. B., wieviel % der p. und wieviel % der e. Dyspepsien im 1. Trimenon auftraten, so stehen den 76,6 % der e. nur 38,2 % der p. Enteritiden gegenüber. Diese Differenz ist statistisch gesichert ($T = 3{,}32$).[1] Das besagt, dass sich die Erkrankungen, bei denen Coli 0 26 gefunden werden, in Bezug auf die Altershäufung genau so verhalten wie die DC-Dyspepsien sonst.

Wie steht es mit dem *Schweregrad* der Erkrankungen? Wir haben oben aus der Literatur einige Angaben zusammengestellt, aus denen hervorgeht, dass 0-26 Dyspepsien nicht so sehr schwer zu verlaufen scheinen. Immerhin darf das nicht zu stark verallgemeinert werden. So fanden z. B. Rantasalo und Hallmann (21) gerade bei den Toxikosen die Coli 0 26 neben den DC 0 111; und auch Braun und Resemann (6) betonen z. B., dass einer der drei schweren ihrer 8 Dyspepsiefälle die schwerste Toxikose seit längerer Zeit überhaupt war. Auch bei den Fällen von Schiavini und Andreoni (22) handelte es sich 5mal um Dyspepsien und 5mal um schwerere Erkrankungen. Krepler und Zischka (13) erwähnen einen Todesfall (bei einem 10 Monate alten Säugling), ebenso Grönroos (9), und McNaught und Stevenson (17) berichten von einem durch die Coli-0 26-Diarrhoe

[1] Bei dem T-Verfahren (H. V. Schelling) ist eine Differenz statistisch signifikant, wenn $T \geq 3{,}0$ ist (27).

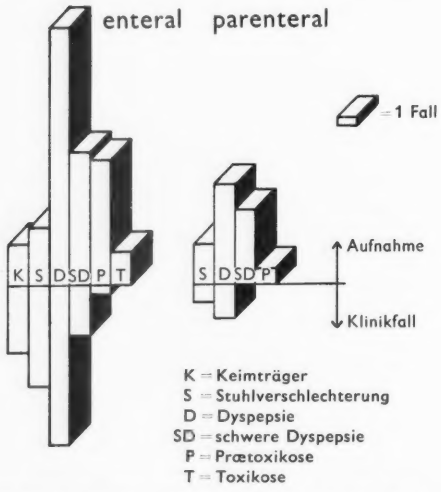

Abb. 3. Verhältnis der zur Aufnahme gekommenen zu den erst in der Klinik entstandenen Coli 0 26-Fälle in den verschiedenen Schweregraden.

beschleunigten Exitus bei einem anderweitig (senile Demenz) erkrankten Erwachsenen.

Die Abb. 3 zeigt die Verteilung unseres Krankengutes in Bezug auf den *Schweregrad*. Wir haben, wie schon in unseren früheren Arbeiten (18,19), auch hier wieder der üblichen Einteilung in Dyspepsie, Praetoxikose und Intoxikation die Kategorien einer blossen Stuhlverschlechterung und die der schweren Dyspepsie hinzugefügt, um das jeweilige Krankheitsbild möglichst präzise zu erfassen. Fälle mit Stuhlverschlechterung sind solche, die noch keine ausgesprochene Dyspepsie haben, bei denen vielmehr ein labiler Zustand besteht, der sich ebenso schnell zur Dyspepsie ausweiten kann wie er sich andererseits durch geeignete Massnahmen schnell normalisieren lässt. Von den landläufigen Dyspepsien haben wir die schweren abgetrennt, bei denen nur noch kein toxisches Symptom zu erkennen war, die andererseits aber wohl meist — in ihrer Entwicklung zur Toxikose — therapeutisch sehr zeitig erfasste Krankheitsbilder waren.

Es ist aus Abb. 3 zu ersehen, dass keineswegs alle 0 26-Fälle leicht verliefen. (So gibt die Abb. 4 als Beispiel den Verlauf einer ausgesprochen schweren Toxikose wieder.) Allerdings ist hier noch eine recht wesentliche Feststellung hinzuzufügen, nämlich die, dass die schwereren Formen in erster Linie bei den *Aufnahmen* zu beobachten waren. Fassen wir nämlich die p. und die e. Durchfallserkrankungen zusammen, so ergibt sich, dass von den 101 Aufnahmen 46 schwer verliefen, d. h. schwere Dyspepsien,

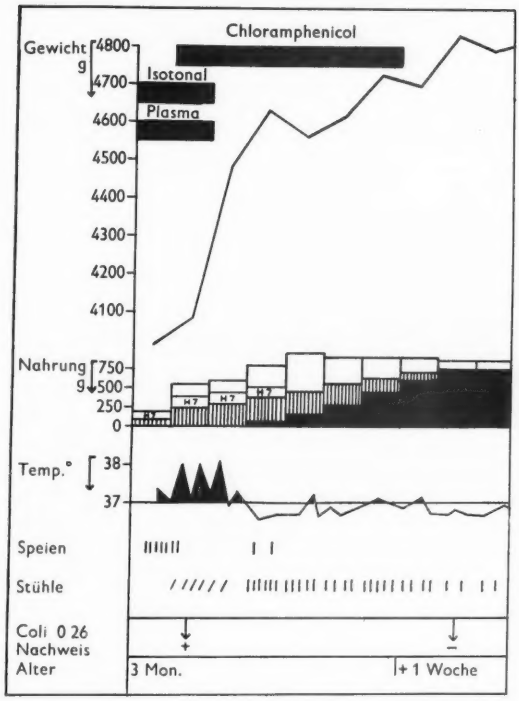

Abb. 4. Verlauf einer durch DC 0 26 ausgelösten Toxikose.

Isotonal = Glucose-Ringer
Hj = Heim-John-Lösung
||||| = Daucaron + Kaukasan
■ = Kaukasan (Trockenbuttermilch)

Praetoxikosen und Intoxikationen waren (= 45,5 %) und von den 44 Klinikfällen nur 7 dieser Gruppe zuzuzählen waren (rund 16 %). Die statistische Berechnung ergibt, dass es sich hier nicht um eine durch den Zufall bedingte Differenz handelt ($T = 3{,}4$). Sie ist leicht mit der in der Klinik weitaus schneller einsetzenden Therapie zu erklären.

Betreffen so die schweren Formen einerseits in erster Linie die Aufnahmen, so sind sie andererseits am meisten bei jüngeren Kindern zu finden, soweit die Erkrankungen rein e. bedingt sind. Hier war kein toxischer Säugling zu finden, der älter als 4 Monate gewesen wäre. Das entspricht genau unseren früheren Feststellungen bei den anderen DC (19). P. renteral ausgelöst kommt dagegen eine schwerere Erkrankung auch bei älteren Säuglingen vor.

Wenn man übrigens auch den Eindruck hatte, dass die e. Erkrankungen relativ schwerer verliefen als die p. Dyspepsien, so lässt sich das jedoch

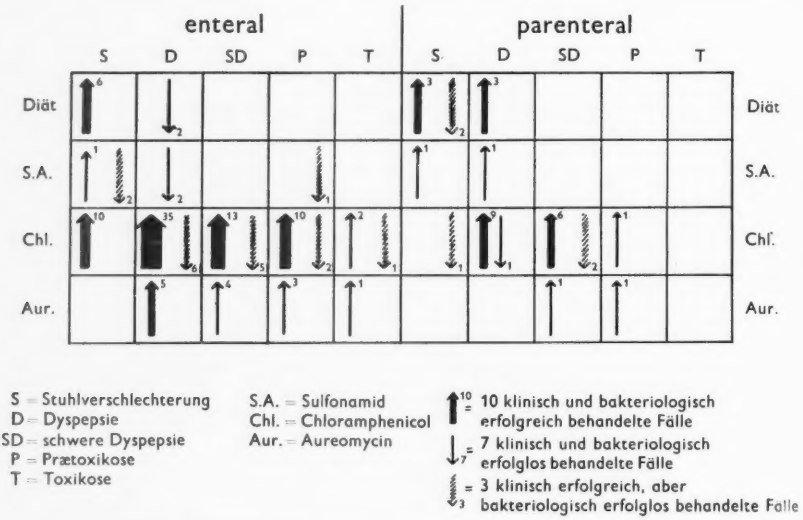

Abb. 5. Therapie und Therapieerfolge bei unserem Krankengut

nicht statistisch sichern. Dass wir in dem ganzen Krankengut keinen Todesfall zu verzeichnen hatten, spricht nicht für eine generell leichte Verlaufsform, sondern vor allem für die rechtzeitig einsetzende, adaequate *Therapie*.

Sie richtete sich weitgehend nach der antibiotischen Resistenzprüfung. Und hier sei kurz eine Bemerkung über die bakteriologische *Methodik* eingeschaltet. Wir führten die Keimisolierung und Identifizierung nach den Prinzipien durch, wie sie in extenso in unserer letzten grösseren Arbeit (19) geschildert worden sind. Wir können darauf mit der Bemerkung verweisen, dass sich diese Technik voll bewährt hat.

Die von uns isolierten 0 26-Stämme gehörten nur zum kleineren Teil dem Typ 0 26 : B 6 : H 11 an, nämlich zu 16,4 %, während alle übrigen unbeweglich waren. Die Unterteilung in Typ 1 und Typ 3 der 0 26 : B 6 : – konnten wir mangels Mannit und Dulcit nicht generell durchführen, so dass wir keine durch grössere Zahlen gestützte Relation zwischen diesen beiden biologischen Typen angeben können.

Was die antibiotische Resistenz anbetrifft, so waren bei uns auch die Coli 0 26, ähnlich wie wir es bei den übrigen DC beobachteten (19), praktisch Streptomycin-unempfindlich, nämlich zu 80 %.

Dass wir nicht generell dem Testergebnis folgen konnten und so z. B., auch wenn im Lochtest der Aureomycinhof grösser als der des Chloramphenicols (Chl.) war, das letztere aus äusseren Gründen wählen mussten, mag vielleicht z. T. begründen, dass wir nicht so gute Erfolge mit Chl. (s. Abb. 5) hatten wie bei der Au.-Anwendung. Wenn man so auch weiss, dass die in einer Klinik anzutreffenden antibiotischen Resistenzen die Art

der örtlich meist verwandten Mittel geradezu widerspiegeln (s. dazu 4) und man daraus hier vermuten könnte, dass die Versager als Folge starker Chl.-Anwendung und entsprechend entwickelter Resistenz zu deuten seien, so ergab sich doch dafür in den Ergebnissen der laufend vorgenommenen Testung noch kein sicherer Anhalt. Immerhin hatten wir auch früher schon darauf hingewiesen, dass uns das Chl. dem Au. unterlegen schien (19), dass sich unter seiner Anwendung die Stühle nicht so prompt besserten und auch Rezidive eher aufträten. Das haben wir bei den Coli 0 26-Dyspepsien wieder gesehen, wobei wir hinzufügen möchten, dass vor allem in einer ganzen Reihe von Fällen (s. Abb. 5) die Stühle erst sehr spät, in 3 Fällen sogar erst nach Wochen, bakteriologisch negativ wurden. Unzweifelhaft wird man aber mit der Gefahr der Resistenzentwicklung rechnen und ihr gegebenenfalls mit dem Wechsel des Antibioticums — adäquat dem Ergebnis der Empfindlichkeitsbestimmung — begegnen müssen.

Weiter ist aus Abb. 5 zu ersehen, dass wesentliche Unterschiede im Therapieeffekt bei den p. und den e. Dyspepsien nicht festzustellen sind.

Bezüglich der Dosierung wäre noch nachzutragen, dass wir das Au. nach wie vor hoch dosiert geben (50 mg/kg et die) und das Chloramphenicol (wir verwandten ausnahmslos das Chloronitrin Jenapharm) in einer Dosis von 80 mg/kg et die. Dabei lösten wir die Aureomycinkapsel zusammen mit Citronensäure (Citrette) in Wasser auf und suspendierten das Chl. in 40 %iger Nährzuckerlösung (Näheres s. 19).

Sind auch gewisse Unterschiede zwischen dem Au. und dem Chl. festzustellen, ist vor allem auch beim Au. über die rein antibiotische Wirkung hinaus noch eine allgemeine stimulierende auf den Säugling vorhanden (s. 19), so sind doch diese Unterschiede gering in Hinsicht auf die ausserordentliche Wandlung der Prognose, wie sie die modernen Antibiotica in der Behandlung der Durchfallserkrankungen gebracht haben.

Schwerere Nebenwirkungen haben wir bei ihrer Anwendung nicht gesehen, abgesehen von sehr häufigem, nach Einbeziehen auch leichter Fälle, jetzt ziemlich generellem Auftreten von Soor nach der Chl.-Gabe, ohne dass daraus schwerere, resp. überhaupt Komplikationen resultiert hätten. Aus dem Rahmen fallende Besonderheiten sind jedenfalls hierüber nicht zu berichten.

Besonders wichtig scheint uns unter unseren Beobachtungen diejenige von einer *Kleinraum-Epidemie*. Sie spielte sich im Januar 1954 in einer in der Nähe Rostocks gelegenen Neugeborenenstation ab.

In den 5 Räumen dieser Abteilung lagen zu dieser Zeit insgesamt 24 Kinder und zwar grösstenteils Neugeborene, zum kleinen Teil auch jüngere Säuglinge. Wir wurden von der leitenden Ärztin dieser Abteilung benachrichtigt und zur Konsultation gebeten, weil innerhalb von 10 Tagen, und zwar *hintereinander, 8 von den 12 Säuglingen* zweier Zimmer mit Durchfall, Erbrechen und Gewichtssturz erkrankt waren.

Bei unserem Besuch ergab sich, dass 2 von den 8 Kindern und zwar die beiden letzterkrankten, eine so schwere Dyspepsie — ohne toxische Zeichen noch — hatten, dass wir sie sofort selbst in unsere Klinik mitnahmen. (Nur sie allein sind in der oben angegebenen Zahl unserer 158 Fälle mitenthalten.) Die übrigen 6 Kinder wurden in der Neugeborenenabteilung selbst sofort mit Chloramphenicol sowie diätetisch und z. T. mit Infusionen behandelt und erholten sich schnell und völlig. Ausser bei diesen 8 Erkrankten machten wir selbstverständlich auch bei allen übrigen 16 Pfleglingen Rectalabstriche. Ausserdem machten wir Abstriche von den Schwesternhänden, den Gerätschaften der Milchküche, von Gegenständen der Pflegezimmer und den persönlichen Pflegeutensilien der Säuglinge und untersuchten schliesslich die Nahrung selbst — alles in der Absicht, möglichst die Infektionsquelle aufzudecken. Am folgenden Tage bekamen wir auch noch die Stühle der pflegenden Schwestern eingesandt.

Zusammenfassend ergab sich folgendes:

1. *Neugeborene.* Bei den oben angegebenen 8 dyspeptischen Kindern fanden sich generell Coli der 0 Gruppe 26 : B 6 : – im Rectalabstrich; sie waren nach Abschluss der Chl.-Behandlung nicht mehr nachzuweisen. Bei weiteren 4 Säuglingen, aber in anderen Zimmern, fanden sich ebenfalls die serol. identischen Colibakterien. Diese 4 Kinder waren am Tage der Untersuchung noch gesund, erkrankten jedoch 1 resp. 3 Tage später ebenfalls mit plötzlichem Gewichtsverlust und Durchfällen, so dass Chloronitrin-Behandlung notwendig wurde, die prompt zur Heilung führte. Insgesamt erkrankten also 12 Kinder und zwar 5 Neugeborene und 7 jüngere Säuglinge innerhalb von 2 Wochen. Wichtig ist noch, darauf hinzuweisen, dass sich in keinem Falle ein Anhalt für einen *grippalen* Infekt usw. ergab, dass es sich also durchweg um enteralbedingte Coli 0 26-Dyspepsien handelte.

Nach Sperren der Station, Entlassung sämtlicher geheilter oder DC-negativer, nicht erkrankter Kinder wurde gründlich desinfiziert. Neuerkrankungen traten daraufhin in der folgenden Zeit nicht mehr auf.

2. *Umgebungsuntersuchung.* Zusammenfassend können wir zunächst sagen, dass wir weder in der Nahrung Coli der 0 Gruppe 26 fanden, noch etwa Keimträger unter den Schwestern, die für die Auslösung dieser Kleinraumepidemie verantwortlich zu machen gewesen wären. Nach unseren Erfahrungen halten wir es nicht für ausgeschlossen, dass die Infektionsquelle bei einer der Mütter zu suchen war, haben wir doch nicht ganz selten bei Neugeborenen schon im ersten Rectalabstrich noch während der Mekoniumzeit DC gefunden. Dass weiter die Keimverschleppung in der Pflege stattfand, zeigten uns die übrigen Ergebnisse: Der Nachweis nämlich von massenhaften Colibakterien in Waschbecken, auf der Waage, am Wickeltisch, in Saugergläsern, weniger in Salbentöpfen, dafür aber wieder reichlich an den untersuchten Schwesternhänden. Diese Befunde, das Fehlen der DC 0 26, *brauchen* nichts zu beweisen, wissen wir doch durch MARGETS Untersuchung (16), dass noch in einem Coligemisch mit 10 %igem Gehalt an spezifischen Keimen deren serologischer Nachweis schon nicht mehr sicher gelingt.

Erwähnt werden muss noch, dass sich auch in der Nahrung, und zwar in einzelnen Flaschen, Colibakterien fanden, jedoch keine der 0-Gruppe 26. Der Ablauf der Epidemie spricht aber ohnehin von vornherein gegen eine zur gleichen Zeit erfolgte alimentäre Infektion, etwa, wie wir sie einmal beobachten konnten (23).

Im Zusammenhang mit dieser Epidemie scheint uns noch interessant, dass gerade aus diesem Ort immer wieder, auch jetzt noch, Dyspepsien und z. T. schwere kommen, bei denen wir Coli 0 26 finden.

Was ergeben sich aus allen diesen Befunden für Schlussfolgerungen? Beginnen wir mit der Frage, ob DC 0 26 bei Säuglingen ein Bild auslösen kann, wie wir es sonst von DC-Dyspepsien gewöhnt sind. Diese Frage dürfte auf Grund der oben in der Literaturzusammenstellung angeführten Einzelbefunde anderer Autoren und des hier in dieser Grösse wohl erstmalig beobachteten Krankengutes schnell und eindeutig zu bejahen sein. Es ergibt sich weiter, dass diese Krankheitsbilder durchaus nicht immer, wenngleich in der Mehrzahl auch bei uns, leicht verlaufen.

Dass hier wie auch sonst eine gewisse Disposition eine Rolle spielen mag, ist nicht zu leugnen. Aber hier gilt das Gleiche, wie das KELLER (11) kürzlich für die generelle Wertung der DC formuliert hat — auch die (enterale) Erkrankung, bei der wir Coli 0 26 finden, wird nicht „ohne den betreffenden Erreger zustandekommen, und das ist das Entscheidende". Wenn man weiter, wie BRAUN (6), die zu Epidemien führende Eigenschaft serologisch fassbarer Colistämme als Voraussetzung für eine Zuordnung zu der Gruppe der säuglingspathogenen Typen betrachtet, so ist gerade die von uns beobachtete Epidemie geeignet, alle Bedenken gegen ein solches Einbeziehen der Coli 0 26 in die DC-Gruppe zu zerstreuen. Sieht man von der besagten Epidemie ab, so spricht ja schon jede Übertragung in der Klinik in gleichem Sinne. Solche Klinikinfektionen sind nicht nur in unserem Krankengut vorgekommen, und zwar wie wir gesehen haben, zu 33 %, sondern auch anderenorts. GRÖNROOS (9) beschreibt 26 seiner 58 0 26-Fälle als in der Klinik entstanden. Und weiter wird in der Arbeit von KUNDRATITZ und GROSS (14) von 15 in der Klinik infizierten Kindern berichtet. MCNAUGHT et al. (17) schliesslich beobachteten sogar eine Infektkette bei Erwachsenen. Nach unseren Erfahrungen können wir deshalb mit BERGER (2) nicht übereinstimmen, wenn er in Bezug auf den Hospitalismus a priori die Gefahr der, wie wir sagen können, DC 0 26 geringer einschätzt als wenn z. B. DC 0 111 in den Stühlen gerade stationär aufgenommener Säuglinge zu finden sind.

Die Zahl der DC 0 26-Erkrankungen hat ganz offensichtlich bei uns zugenommen, wie wir sahen. (Auch bei Erwachsenen haben wir übrigens, ohne hier näher darauf eingehen zu wollen, in 12 Fällen DC 0 26 gefunden.) Ob damit auch eine Virulenzschwankung verbunden ist, können wir nicht, resp. aus dem Fehlen entsprechender andernorts gemachten Beobachtungen, *noch* nicht sagen. Für ausgeschlossen halten wir eine solche Schwankung nicht, die dann nicht nur die Kontagiosität, sondern auch die Pathogenität betreffen könnte.

Interessant ist in diesem Zusammenhang ein Detail aus dem Material von GRÖNROOS (9). Er berechnet die statistische Signifikanz für den Frequenz-Unterschied der DC 0 55 bei Dyspepsien und bei Keimträgern und

findet, dass er zufallsbedingt sein kann. Damit wäre die Rolle der Coli 0 55 als DC, die doch allgemein anerkannt wird, anzuzweifeln. Die Erklärung für diese Unstimmigkeit liegt dabei wohl darin, dass die zugrundeliegenden Zahlen sehr klein sind.

Möglicherweise hat entsprechend gerade die bisherige Seltenheit von DC 0 26-Befunden auch deren Wertung innerhalb der DC-Gruppe erschwert. Ähnliches mag z. B. ebenfalls für gewisse Coli der 0-Gruppe 25 gelten, die wir — auf Grund der Beobachtung einer kleinen Epidemie — der DC-Gruppe zuzählen möchten (18, s. dazu auch 5), Colitypen, die wir in der letzten Zeit jedoch weniger isolieren.

Zusammenfassung

Bisher wurden Coli der 0-Gruppe 26 nur wenig und meist bei sporadischen Fällen von Säuglingsenteritis gefunden. In der vorliegenden Arbeit wird auf die auffällige Zunahme dieser Colitypen in unserem Krankengut hingewiesen und die Beschreibung von insgesamt 158 Fällen gegeben. Die Beobachtung einer Kleinraumepidemie und die nicht kleine Zahl erst in der Klinik stattgefundener Übertragungen geben uns Anlass, die Bedeutung auch dieser Dyspepsiecoli für den Hospitalismus nicht zu gering zu veranschlagen.

The Prevalence of Bact. Coli 0 26 in Infantile Diarrhoea.

In the Pediatric Clinic of Rostock, East-Germany, B. Coli 0 26 were occasionally found in cases of infantile diarrhoea. These Coli types have now become very frequent and have been observed in 158 cases. An epidemic within a small-room ward was studied, some cases becoming infected while in the hospital. The importance of these dyspepsia Coli for cross-infections in hospital wards should not be underestimated.

La fréquence du Bact. Coli 0 26 dans la diarrhée du nourrisson.

A la clinique pédiatrique de Rostock, Allemagne Orientale, le Coli 0 26 n'a été trouvé que rarement et dans des cas sporadiques de diarrhée infantile. Ces types de Coli sont maintenant devenus très fréquents et on les a rencontrés dans 158 cas. On a examiné une épidémie dans deux petites salles et assez bien de cas devinrent infectés pendant l'hospitalisation. On ne peut sousestimer l'importance de ces Coli de dyspepsie pour le développement de l'hypothrepsie hospitalière.

El bacilo Coli 0 26 en diarrea infantil.

En la Clínica Pediátrica de Rostock, Alemania del Este, se encontró el Bacilo Coli 0 26 solamente en raros y esporádicos casos de diarrea infantil. Este tipo de Coli se ha vuelto actualmente muy frecuente y fué observado en 158 casos. Se estudió una epidemia en dos pequeñas salas y se encontró que varios casos en el hospital se infectaron durante ese período. No debería subestimarse la importancia de esas dispepsias a Bac. Coli en el desenvolvimiento de hospitalismos.

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The Prevalence of Cerebral Palsy

by GILLIS HERLITZ *and* BJÖRN REDIN

When planning a programme for the children with cerebral palsy in a certain district, it is necessary first to know the incidence of the disease within this district and the distribution of cases with regard to the possibility of treatment. In the literature on cerebral palsy the reported frequences vary greatly, from causes which are not entirely known at present. Thus, in an investigation from England (2) an incidence of about 1 per 1000 among the school age population is reported, while an American investigation (7) indicates the prevalence to be four times as great. Other American figures (9), however, are lower: one case surviving among 568 live births. An earlier Swedish investigation (6) reports a frequency of 0.6 per 1000 seven-year-old children. Other Scandinavian authors (1, 10), in field investigations in Denmark and Norway, have found values approaching 150/100,000 of the total population but have estimated the probable real incidence to be about 50 per cent higher. This estimate is based upon calculations from the 5-year group where the highest figures have been observed. A similar mode of estimation has also been used by American authors. The English figure quoted above only applies to the frequency of cerebral palsy actually observed in the age group 5–15 years in a particular district.

Most authors, in estimating the prevalence of cerebral palsy in 100,000 individuals of the total population from the incidence in a certain age group (usually 5–9 years), have directly applied the observed mean number of cases in the age groups concerned to the total population, thus getting a figure for the number of new cases every year in 100,000. This figure has then been multiplied by the number of years which corresponds to the average duration of life within the population, thus giving the prevalence, expressed in the number of cases of cerebral palsy in 100,000 of the total population.

This way of calculation is based upon two important conditions: (1) cerebral palsy has had the same frequency in earlier years as it has now, and (2) the life expectancy is the same for the cases of cerebral palsy as for the general population.

In practice, neither of these conditions is a certainty. Since many of the palsy cases are recruited from the premature children, which probably, nowadays, survive to a far greater extent than before, a higher incidence can be expected from this cause alone. Proper knowledge of the average duration of life in cerebral palsy is lacking. All probability points to its being less than that of the general population. If they were better known, these factors might change the figures considerably. Nor is the fact to be disregarded that many of the mild cases gradually improve or may even recover completely.

It should also be emphasized that if the figures for the prevalence of cerebral palsy per 100,000 of the total population from different countries, calculated in this way, are to be compared, the average duration of life on which the figures are based must also be taken into consideration. Scandinavian authors have counted on a life expectancy of 65 years, while PHELPS (8) has given the figure 40 years for his cases of cerebral palsy.

Furthermore, it is hardly correct, and likely to cause misunderstanding, to express the frequency of cerebral palsy in the number of cases born yearly in a population. How many cases that are born is beyond our estimation, only those surviving can be counted. Of the palsy cases, 20–40 per cent are prematures (the figures vary). In a material from the last few years of 275 babies in our premature department, 72 died, 66 of them during the first week of life. It is evident that among these 66 prematures there were several potential palsy cases which never came to light. It is also to be pointed out that 5–10 per cent of the palsy cases (1, 2, 9, 10) are acquired postnatally (the cases of kernicterus not included).

A clearer conception of the situation is obtained from the figures expressing the incidence as the number of surviving cerebral palsy cases per 1000 live births in a certain population, or, still better, from the figures giving the incidence in 1000 individuals of every year-group or 5-year group investigated. Both methods make it possible to compare directly the conditions in different countries.

One point in this connection, chiefly concerning the clinical aspect, is this: if one obtains material in a field study, including only $^2/_3$ of the palsy cases which should exist within that part of the population, based on estimations from the year-group showing the highest incidence, the representativity of this clinical and statistical material must be questioned. What cases will be missing? It may be presumed that sometimes the mildest but sometimes also the most severe in this way escape the investigation.

In order to get a correct conception of the incidence and the distribution of clinical types of cerebral palsy in a population, it is evidently of

the greatest importance to trace, as far as possible, all the cases, or to limit the statistical calculations to the year groups showing the highest incidence.

Proceeding from these considerations we have made an inventory of the cerebral palsy cases in the Östergötland county (total population at the time of the investigation 265,670 people, 40 per cent living in towns). We have limited the investigation to ten year-groups, namely 2–11 years. Below 2 years of age the diagnosis of the disease is sometimes difficult, and in some cases symptoms are not yet apparent. About one half of the 10-year group fall within the school age, while the other half consist of pre-school children.

The county (including its towns) is divided into 59 districts with a district nurse in each, who, as a rule, knows well the state of health of the children in every family within the territory of about 4500 people under her supervision. From all these nurses information has been obtained through questionnaires. Generally, the answers have been given after consultation with the district doctor. Furthermore, information has been requested from all the 46 primary school boards, which register all children entering school age, 45 boards of children's welfare, and 155 parish registration offices (the clergymen often have a good knowledge of the families within their parish and have the mentally subnormal registered). All these authorities have answered with the exception of one parish office. The doctors of 14 large schools have received an inquiry and all have answered. The Child Welfare Centers of the 6 towns have also been written to and have answered. All institutions and schools for mentally subnormal children in the county have been checked, including the records of admitted, discharged and expected children, the majority of whom have been examined by us for this investigation. The county has only one hospital for children, in which the in-and-out patient records have been reviewed. For the three-year period since the establishment of the only orthopaedic department in the county, information has also been collected.

Since it may be presumed that some unknown palsy cases hide among the mentally subnormal children, an account of the latter has always been asked for in the inquiries above. The slightest suspicion of cerebral palsy has led to an examination by us. At least 6 cases of cerebral palsy, not observed previously, have been discovered in this way, 4 of which were in institutions for mentally subnormal children.

All children with cerebral palsy, verified or suspected, have been examined by us with few exceptions, usually those cases admitted to institutions outside the county. Information concerning the circumstances at birth has been received from the institutions where the children were born. In 96 per cent of the 84 cases, in which the birth place was known, the delivery occurred at an institution.

The results of the investigation are accounted for below. In those cases where information has not been complete the term "unknown" has been used.

TABLE 1

Distribution of cases according to sex and age.

Age years	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–11	11–12	Total
♂	3	5	9	3	6	3	11	4	2	5	51
♀	5	6	5	5	3	2	4	7	3	5	45
Total	8	11	14	8	9	5	15	11	5	10	96

Incidence. The total number of cerebral palsy cases discovered is 96 (Table 1). At the time of the investigation, the total number of children in the age group 2–11 years in the population was 46,100, approximately equally distributed between these 10 year-groups. Table 1 shows an average of 9.6 children per year-group, or 2.1 cases of cerebral palsy per 1000 children in the age groups studied. Obviously, in our material the age groups from 5–9 years do not show any over-representation. This is, to a certain extent, a guarantee that our round-up has been complete. Also 38 of the cases come from towns, which is the same distribution as that of the total population. The beginning of school age is not accompanied by any increase in frequency. The material, therefore, ought to be representative enough to allow an analysis of the disease within the younger ages in this county.

Clinical classification is given in Table 2. For comparison the figures of some other authors are quoted in Table 3. The last three authors of the Table, at least, have obtained their figures from field investigations such as those employed in this study.

Our low frequency of pure athetosis and our high frequency of spasticity is striking. The first-mentioned, at least, cannot be due to mere chance.

TABLE 2

Type distribution in the present series. Number of cases.

Spasticity										Athetosis		Ataxia		Atonic types		Mixed types	
Mono-plegia		Para-plegia		Tri-plegia		Quadri plegia		Hemi-plegia									
♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
2	3	13	20	2	—	7	7	21	10	1	1	2	1	—	1	3	2
5		33		2		14		31		2		3		1		5[1]	

[1] spasticity + athetosis 4, spasticity + ataxia 1.

TABLE 3

Type distribution in various surveys.

	Spasticity, %	Athetosis, %	Ataxia %	Atonic types, %	Rigidity %	Tremor %	Mixed types, %	Other types, %
Present series . . .	88.6	2.1	3.1	1.0	—	—	5.2	—
Phelps	40.0	40.0	20.0	—	—	—	—	—
Pohl	66.0	19.0	8.0	—	4.0	2.0	1.0	—
Hohman	61.0	24.0	4.0	—	—	—	10.0	—
Nilsonne	72.0	23.0	2.5	—	2.5	—	—	—
Asher and Schonell	83.0	10.0	1.0	0.6	0.3		5.0	—
Scheel-Thomsen . .	77.1	9.3	6.8	—	0.9		4.2	1.7
Andersen	65.0	19.5	11.7	—	2.6	1.3	—	—

In so far as the difference is not due to the fact that the materials may not be fully comparable (some of them being derived from institutions) or to our relatively high frequency of mixed types in which athetosis is a component, other explanations may be postulated. ASHER and SCHONELL (2), among their athetoids, found a remarkable incidence of severe jaundice, namely 33 per cent, the cases of kernicterus excluded. The latter included, the figure rose to 55,6 per cent. Among our children we have no cases of Rh-incompatibility and only 2 cases with pronounced jaundice, both spastics without athetosis. It seems possible that other similar states of jaundice secondarily affecting the basal ganglia, with or without liver damage, are less common in our county. As apposed to the ataxic type, the athetotic one is not so easily overlooked in a field investigation. The sinking relative frequency of athetosis is accompanied by an increase in that of spasticity.

Child rank. Several authors have found a preponderance of the firstborn among the children with cerebral palsy. We have 50.6 per cent firstborn in our material. Others (2, 9) have expressed the opinion that parents who had one child with cerebral palsy are likely to stop having children. The figure for the firstborn, then, gets a limited value, further stressed by the fact that hereditary factors cannot be excluded among the etiological elements.

Twins occur in 3 cases in our material. All the 6 twins had a birth weight below 2,500 g. In none of the cases has cerebral palsy with certainty been demonstrated in the other twin, since 3 of them died shortly after birth.

The mother's state of health during pregnancy is accounted for in Table 4. In 15.7 per cent the mother was ill during pregnancy.

TABLE 4

The mother's state of health during pregnancy. Congenital cases.

	♂	♀	Total
Diabetes		1	1
Eclampsia	2	2	4
Nephropathy with hypertension		2	2
Pyelitis		1	1
Hyperthyroidism		1	1
Parotitis		1	1
Lues		1	1
Heart failure[1]	1		1
Haemorrhages	1		1
Ill	4	9	13
Well	41	29	70
Unknown	5	4	9
Total	50	42	92

[1] Died during labour.

The obstetrical history is given in Table 5. In 36,8 per cent it was abnormal. Labour has been considered prolonged if it has exceeded 36 hours.

TABLE 5

Obstetrical history. Congenital cases.

	♂	♀	Total
Prolonged labour	6	4	10
Fast labour (1 ½ hour, primipara)	1		1
Forceps	6	2	8
Sectio caesarea	1		1
Breech delivery	4	5	9
Foot delivery		1	1
Asphyxia imminens	1		1
Real knot of the umbilical cord	1		1
Abnormal obstetrical history	20	12	32
Normal obstetrical history	28	27	55
Unknown	2	3	5
Total	50	42	92

The birth weight is accounted for in Table 6. In 28,7 per cent the weight at birth was below 2,500 g. Of the 25 prematures, 21 belonged to the spasticity group, which is thus recruited to $^1/_4$, at least, from the premature children.

TABLE 6

Birth weight. Congenital cases.

	♂	♀	Total
<2,500 g	10	15	25
2,500—4,000 g	33	23	56
>4,000 g	5	1	6
Unknown	2	3	5
Total	50	42	92

Symptoms of brain damage during the first week of life (cyanosis, convulsions, paralysis, cerebral cries, marked restlessness, pallor, slackness, rigidity, apathy, bulging fontanel) occurred in 48.3 per cent.

Etiological factors. The percentage of acquired cases has been estimated (1, 2, 9, 10) at 5 to 10 per cent. In our material only 4 definite cases of this kind occurred (trauma 2, gastroenteritis with toxemia 1, encephalitis 1). They have been excluded from the calculations above, which concern the mother's health during pregnancy and the circumstances at birth. The toxemic case belongs to the atactic group and has an intelligence quotient (I.Q.) below 30, the other three belong to the spasticity group and have normal intelligence.

The most frequently observed etiological factors in the congenital cases are prematurity, the mother's illness during pregnancy, and an abnormal obstetrical history; while malformations, heredity and blood incompatibility are usually noted in second place. In our material we have two cases of hydrocephalus, but otherwise no instance of the three last-mentioned factors. The overwhelming importance of the three first-mentioned etiological factors is evidenced by the fact that the number of our cases in which one or more of these factors has obviously had a possibility to assert itself, amounts to 55 in 83 cases, i.e. to 66,3 per cent, the acquired cases and those in which all factors were not known being omitted.

It is generally stated that asphyxial conditions in the newborn are one of the most common causes of the brain damage which produces cerebral palsy. This can hardly be denied, but to ascertain in each case, whether the asphyxia is a cause or merely an effect, will as a rule be very difficult. Even the mucus in the throat, which appears to prevent respiration, and

the eliminating of which results in efficient respiratory movements, may sometimes be only a symptom of some brain damage already established.

The question whether the administration of general anaesthetics to the mother during labour might have a causal connection with cerebral palsy in the child, is rather important. However, our present information does not permit any conclusions on this point. It is striking that the three primary etiological factors mentioned above often combine in our series, e.g. diabetes–forceps, eclampsy–premature, breech delivery–premature, and so on. In those cases where the mother had been given general anaesthetics, it seems that other etiological factors must also be taken into consideration.

Since the brain injuries causing cerebral palsy in the premature children probably arise so early in the extrauterine life that they cannot be prevented, and since the modern care of premature children, through prophylaxis, therapy against infections, etc., will result in a larger percentage of survivors, there is evidently reason to consider the possibility of a relative increase in cerebral palsy in the general population.

Intelligence. The difficulties in obtaining proper psychological evaluations of a cerebral palsied child with ordinary tests for estimating I.Q. are stressed by most authors who have been occupied with this problem. However, some authors (2, 4, 5) have found a few of the tests suitable in most cases. According to DENHOFF (3), an equally good conception can be obtained from extended observations of the children socially, developmentally and adaptively. MILLER and ROSENFELD (5) got the same distribution of intelligence with subjective evaluation as with testing. We have refrained from attempts to get a psychological evaluation of the children in our series on the basis of intelligence tests alone and have estimated the intelligence level mainly from the results of trials at teaching and the collected general observations of the children's mental capacity.

Mental defects, corresponding to I.Q. < 70, occurred, according to this evaluation, in 55 children in our series (57,3 %), and of these 37 (38,4 %) were of low grade mentality (I.Q. < 50). These figures are somewhat higher than those of the other Scandinavian materials and approach the figures of HOHMAN (4) from North Carolina (60 and 40 % respectively).

Summary

The methods of estimating and indicating the prevalence of cerebral palsy in a population are critically discussed. A survey is given of the occurrence of cerebral palsy in a 10-year group of a population of 265,000 individuals in Sweden. The incidence of cerebral palsy was here 2.1 per 1000 children in the ages 2–11 years. In two thirds of the cases prematurity, illness of the mother during pregnancy or an ab-

normal obstetrical history was shown to have been present. Mental defects, corresponding to I.Q. <70, occurred in 57 per cent and low grade mentality (I.Q. <50) in 38 per cent of the cases.

La fréquence des encéphalopathies chroniques de l'enfance.

L'auteur discute les méthodes employées pour estimer et déterminer la fréquence de la paralysie par encéphalopathie dans une population. On a étudié la fréquence de la paralysie par encéphalopathie dans un groupe d'enfants âgés de dix ans parmi une population de 265.000 habitants en Suède. Elle était de 2,1 pour mille enfants âgés de 2 à 11 ans. Dans deux tiers des cas on a retrouvé dans l'anamnèse la prématuration, une maladie de la mère pendant la grossesse ou des difficultés obstétriquales à la naissance. Dans 57 % des cas il y avait une déficience mentale correspondant à un quotient d'intelligence inférieur à 70, dans 38 % des cas il y avait débilité mentale marquée (quot. d'intell. inférieur à 50).

Die Verbreitung der cerebralen Kinderlähmung (Morbus Little).

Die Methoden zur Schätzung der Verbreitung der cerebralen Kinderlähmung in einer Bevölkerungsgruppe werden kritisch beurteilt. Es wird ein Überblick über die Häufigkeit der cerebralen Kinderlähmung in einer 10 Jahre umfassenden Bevölkerungsgruppe von 265000 Einwohnern in Schweden gegeben. Die Häufigkeit der cerebralen Kinderlähmung betrug hier 2,1 pro 1000 Kinder im Alter von 2–11 Jahren. In zwei Drittel der Fälle fand man Prämaturität, Krankheit der Mutter während der Schwangerschaft oder einen anormalen Geburtsverlauf. Geistige Defekte, einem I.Q. <70 entsprechend, traten in 57 % der Fälle auf, und Geistesschwäche (I.Q. <50) in 38 % der Fälle.

La incidencia de parálisis cerebral.

Se discuten los métodos de estimación de la incidencia de parálisis cerebral en una población. Se relata un estudio de la ocurrencia de parálisis cerebral en un grupo de personas cuyas edades abarcaban un período de 10 años, en una población de 265.000 individuos, en Suecia. La incidencia de parálisis cerebral fué de 2,1 por 1000 niños en las edades de 2 a 11 años. En dos tercios de los casos se encontraron prematurez, enfermedad de la madre durante la gravidez o una historia obstétrica anormal. Defectos mentales correspondiendo a I.Q. 70 se encontraron en 57 % y una mentalidad de bajo grado I.Q. 50 se encontró en 38 % de los casos.

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CASE REPORTS

Galactosaemia

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From the Pediatric University Clinic of the Municipal Hospital, Aarhus, Denmark
(Head: Professor Bent Andersen)

A female infant, K. H., was admitted to the Pediatric University Clinic of Aarhus Municipal Hospital on September 1, 1952.

The father was 24 years and the mother 25 years of age; both in good health, not related. There were no known cases of metabolic disorders in the family, and no infant deaths had occurred during the last two generations.

The patient was the only child of the family; the mother had been in good health during the pregnancy; normal delivery, weight at birth 2,800 g, length 49 cm. No asphyxia; the baby took the breast at once; breast-feeding was continued for two weeks; then a supplementary milk formula was given for one week, after which time the baby was put on a dilute milk formula.

During the first fortnight of life the infant appeared to be normal, but then became languid and drowsy. She was admitted to a regional hospital at the age of three weeks, at which time she had lost 470 g in weight since birth. Jaundice was present until the infant was one month old. She was very languid and took her feedings poorly; no diarrhoea or vomiting.

Owing to the presence of sugar in the urine (approx. 1 %), the patient was given insulin (max. 8 I.U. in 24 hours). As hypoglycaemic reactions developed, the insulin dose was gradually decreased to 3 I.U. The excretion of sugar in the urine persisted unchanged, and only a slight fall in the blood-sugar level occurred. A tentative diagnosis of galactosaemia was considered, but a study of the urine performed on one occasion failed to reveal galactose. An ophthalmological examination disclosed the presence of nuclear cataract. As, at the age of 5 months, the weight was only 750 g more than at birth, the patient was transferred to this clinic.

On admission here, physical examination revealed a poorly developed and poorly nourished, flabby infant (length 58 cm), perspiring profusely. She did not stir, did not even turn the head; nor did she smile or show other signs of mental activity (Fig. 1).

There were no signs of rickets, and auscultation did not reveal any abnormalities. The liver was smooth and firm and extended to the level of the umbilicus; the spleen was not palpable.

The extremities showed diminished muscular tone, and the deep reflexes were weak.

Ophthalmological examination: The patient did not fix her attention on objects or persons. The eyeballs moved incessantly from side to side. Both lenses showed a greyish cataractous opacity posteriorly.

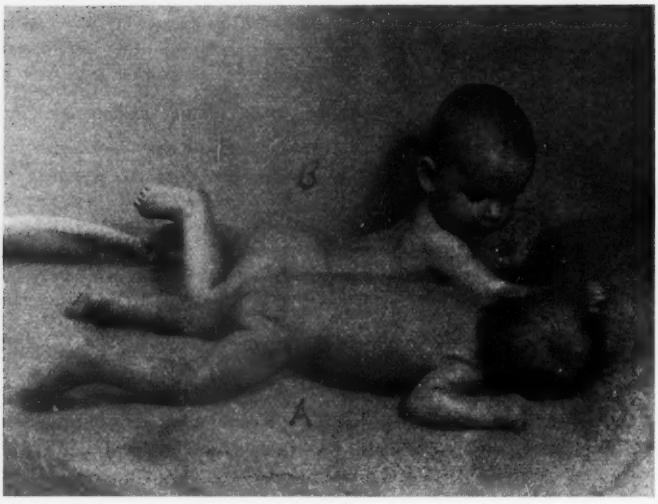

Fig. 1. Patient (*A*), at the age of 8 months, shown together with healthy infant of the same age (*B*).

The baby was fed a dilute milk formula (80 %) with added protein, and gruel. As she was taking feedings poorly, she had to be fed by gavage and then, slowly, she began to gain weight.

Albumin (approx. 2 %) and sugar (approx. 1.5 %) were constantly present in the urine, and fasting blood-sugar readings varied between 150 and 200 mg %. Insulin LEO retard, 2 I.U. in the morning and 1 I.U. in the evening, was administered. The condition remained unchanged, and the weight increased very slowly.

On Sep. 20, the sugar excreted was identified as galactose, for which reason insulin was withdrawn and milk was removed from the diet. The next day, the urine did not contain sugar or albumin, and the fasting blood-sugar reading was normal. During the next few days the liver decreased considerably in size.

Shortly afterwards, milk was resumed for a short period with a view towards further investigations. When milk was again omitted from the regimen, galactose disappeared from the urine within 12 hours, followed by a transitory glucosuria.

As soon as the patient was placed on a milk-free diet, a spectacular improvement occurred. She gained weight rapidly and the length increased by 5 cm during the first six weeks. A few weeks later she was alert, and her spontaneous activity had greatly increased; she began to turn the head and sweating became less profuse (Fig. 2). This development continued throughout the hospital stay.

Fever without any known cause developed on several occasions, once in direct association with a galactose tolerance test, but a repeated tolerance test was not followed by any rise in temperature.

Bone roentgenograms, taken when the patient was 7 months old and still receiving milk, showed considerable halisteresis and a very thin cortex. When the infant was placed on a milk-free diet, the halisteresis diminished, and at the age of 16 months the bones showed normal conditions.

Fig. 2. Patient, at the age of 11 months.

Fig. 3. Patient, at the age of 15 months.

At a follow-up examination after 8 months on a milk-free diet, the patient was able to pull herself up to a sitting position almost unaided and attempted to stand. She was alert, could take hold of toys and shake hands when called upon to do so. The eye movements were almost normal, and there were no signs of cataract. The liver was felt as a small, firm mass below the right costal margin. Weight 8,550 g; length 72 cm.

Laboratory Findings

a. Patient on milk diet

Urine. — Galactose was analyzed by paper chromatography and by determination of the melting point of the osazone prepared. Amino acids, which were excreted in large amounts, were demonstrated by paper chromatography. (For the methods used and the results obtained in these analyses, see DARLING and MORTENSEN.) Albumin was demonstrated by Heller's test. Calcium was demonstrated by Sulkowitch's reaction, which resulted in distinct precipitation. Nitrogen (Kjeldahl), 11.53 mg/ml, average for 9 days. No ketone bodies (Gerhard and Legal). Microscopic examination revealed some granular casts.

Blood. — The total reduction was determined by the technique of Hagedorn-Jensen. Galactose was determined as described by ALTHAUSEN *et al.* On three different days the findings (after 7 hours of fasting) were as follows: –

Total reduction mg%	Reduction after fermentation mg%	Difference mg%
215	138	77
179	118	61
186	124	62

Haemoglobin, 70–80 %. Volume and colour indices, approx. 1. Leukocytes, 10,000–20,000; differential count normal. Seroreaction for syphilis negative. Serum calcium, 10 mg %. Serum phosphorus, 6.1 mg %. Serum phosphatase (Lundsteen and Vermehren) normal. Serum potassium, 4.42 mEq./litre. Takata-Ara test negative. Thymol reaction negative. Serum proteins (Henriques and Klausen), 5.5 %. Albumin, 4.2 %; globulin 1.3 %. Relative distribution (paper electrophoresis was carried out by Dr. P. BJERRE HANSEN): Albumin + α_1-globulin 78 %, α_2-globulin 10 %, β-globulin 8 %, γ-globulin 4 %.

Tuberculin test negative. Bone marrow normal. Insulin test (after 7 hours of fasting): –

Time	Total reduction
0.00	120 mg%
0.30	125 ,,
1.15	Subcutaneous insulin, 6 I. U.
2.00	97 mg%
3.00	70 ,,
3.25	Unconscious with generalized convulsions. Symptoms disappeared after administration of glucose by stomach tube.

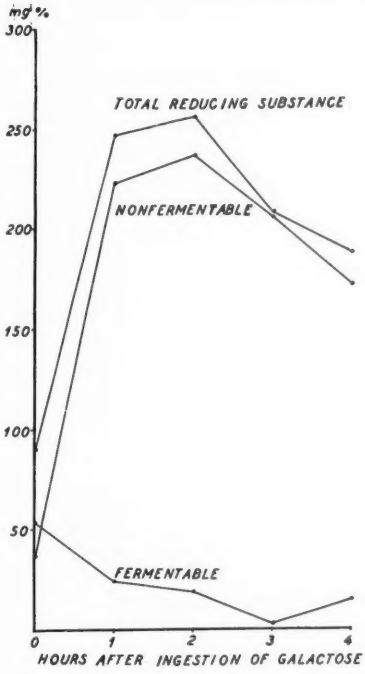

Fig. 4. Galactose tolerance curve after oral administration of 1.75 g galactose/kg.

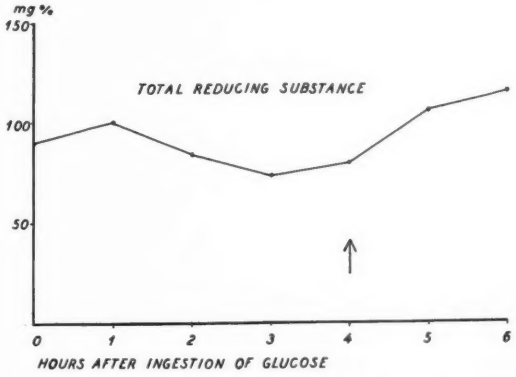

Fig. 5. Glucose tolerance curve after oral administration of 1.75 g glucose/kg. At arrow injection of 0.2 ml of ephedrine solution.

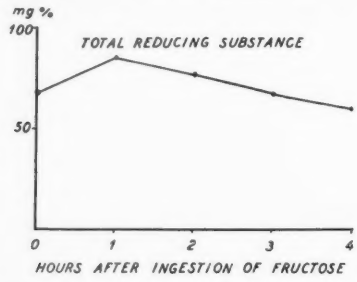

Fig. 6. Fructose tolerance curve after oral administration of 1.75 g fructose/kg.

Spinal fluid (Bisgaard): Albumin, 32 (normal 10). Globulin, 3 (normal 1). Cells, 4 per cmm. Total reduction (Hagedorn-Jensen): 100 mg %. In the blood, at the same time, 186 mg %. Fermentable fraction: 19 mg %, 62 mg % (in the blood).

b. Patient on milk-free diet

Urine contained no sugar or albumin. Amino-acid excretion considerably decreased, but not normal (see DARLING and MORTENSEN). Sulkowitch negative. Urine nitrogen, 2.74 mg/ml (average for 11 days). Galactose tolerance test pathological, see Fig. 4. Glucose and fructose tolerance tests normal, see Figs. 5 and 6. (The tests were carried out after 7 hours of fasting.)

Serum potassium, 4.23 mEq./litre. Serum sodium, 140 mEq./litre. Blood urea normal. Fasting blood sugar, 85–125 mg %. Spinal fluid, 1 cell per cmm.

Albumin, 20. Globulin, 0.

Discussion

Our patient presented typical manifestations of galactosaemia: failure to thrive, mental retardation, hepatomegaly, cataract, osteoporosis, galactose in the blood, and excretion of galactose and albumin in the urine. To confirm the diagnosis, a galactose tolerance test was performed, resulting in a marked increase in total blood sugar. During this experiment a pronounced fall in the glucose content of the blood was demonstrated, which is of interest, because the same phenomenon has been observed by several other writers (e.g. LANGEWISCH and BIGLER, GOLDSTEIN and ENNIS, GOLDBLOOM and BRICKMAN). However, we dared not rely on this finding, because it was not accompanied by any clinical signs of hypoglycaemia. The result must be supposed to be due to an error in the analysis, possibly defective fermentation. On administration of insulin, the fall in the blood-sugar level was accompanied by convulsions, which rapidly subsided after medication of glucose.

The osteoporosis, which has also been observed by a few other writers (GOLDBLOOM and BRICKMAN, MASON and TURNER, NORMAN and FASHENA), may be explained by the demonstrated loss of calcium through the urine. When this ceased the calcium content of the bones returned to normal.

As already mentioned, the considerable excretion of amino acids in the urine has been discussed in another paper (DARLING and MORTENSEN). The amino-aciduria may have been a contributory cause of the retardation of physical growth.

We want to call attention to the difference in the nitrogen content of the urine before and after the removal of milk from the diet, but as the exact nitrogen content of the diet is not known, nothing can be said as to the nitrogen equilibrium.

Increased spinal-fluid protein was also demonstrated in BRUCK and RAPOPORT's patient. In our patient, the protein content decreased considerably during treatment.

When milk was removed from the diet, galactose disappeared from the urine within 24 hours, for a short period superseded by glucose. It is a striking fact that the albuminuria disappeared just as rapidly.

The rapidity with which the liver decreased in size was also striking. However, some hepatic enlargement persisted. The explanation may be that the fat content of the cells disappears, while the cirrhotic changes remain unchanged.

Considering that therapy was initiated relatively late, viz. at the age of 6 months, it is surprising that the cataract cleared completely. From a study of the literature, REITER and LASKY concluded that the cataract can only be expected to be overcome if the infants are placed on a milk-free diet within the first three months of life.

It is difficult to say anything definite as to the final prognosis; the presence or absence of irreversible damage to the central nervous system will be of decisive importance for the mental development and the liver cirrhosis for the outlook in general.

Summary

A case of galactosaemia is reported. The patient was a 5-month-old girl with typical symptoms of the disease. The galactose tolerance was reduced, and galactose could be demonstrated in the urine both by chemical methods and by paper chromatography. The excretion of calcium and amino acids in the urine, and the protein content of the spinal fluid were increased. When milk was removed from the diet, considerable physical and mental development occurred and the cataract disappeared. The excretion of galactose and albumin in the urine ceased and the excretion of calcium and amino acids decreased.

Galactosémie.

Les auteurs rapportent un cas de galactosémie. Il s'agissait d'une fille de 5 mois présentant les symptomes typiques de la maladie. La tolérance au galactose était réduite et il était possible de mettre en évidence la présence de galactose dans les urines chimiquement et également par la méthode chromatique sur papier. L'excrétion du calcium et des aminoacides était augmentée dans les urines ainsi que l'albumine dans le L.C.R. On observa un développement considérable tant physique que mental et une disparition de la cataracte dès la suppression du lait de l'alimentation. L'excrétion du galactose et de l'albumine dans les urines cessa et l'excrétion du calcium et des aminoacides diminua.

Galaktosämie.

Es wird über einen Fall von Galaktosämie berichtet. Es handelte sich um ein 5 Monate altes Mädchen mit typischen Krankheitssymptomen. Die Galaktose-Toleranz war reduziert, und Galaktose konnte im Urin sowohl chemisch als auch mit der Papier-Chromatographie nachgewiesen werden. Die Ausscheidung von Calcium und Aminosäuren im Urin war erhöht und ebenso der Proteingehalt des Liquors. Wenn

man der Diät Milch entzog, kam es zu einer bedeutenden physischen und geistigen Entwicklung und der Katarakt verschwand. Die Ausscheidung von Galaktose und Albumin im Urin hörte auf, und es kam zu einem Herabsinken der Calcium- und Aminosäurenausscheidung.

Galactosemia.

Se relata un caso de galactosemia. La paciente fué una niña de 5 meses con síntomas típicos de la enfermedad. La tolerancia a la galactosa estaba reducida y se pudo demostrar la presencia de dicho azúcar en la orina por métodos químicos y papel cromatográfico. Estaba aumentada la excreción de calcio y aminoácidos en la orina y también el contenido proteico del líquido cefalorraquídeo. Cuando se quitó la leche de la alimentación se observó un considerable desarrollo mental y físico y desapareció la catarata. La excreción de calcio y aminoácidos declinó.

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See the references listed in the authors' paper "Galactosemia", Acta Pædiatrica *43*. 467, 1954.

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From the Pediatric Department of Sundby Hospital, Copenhagen
(Chief: Senior Physician CARL FRIDERICHSEN, M.D.)

A Case of Congenital Polycystic Kidney in a Child

by IRENE OLESEN

In children beyond the neonatal period, polycystic kidney is a very rare disorder; the writer therefore considered that it would be justifiable to report the following case of the disease in a girl who is now 5 years old and who has previously, in 1951, been described in *Dansk Pædiatrisk Selskab* by C. FRIDERICHSEN.

A survey of the age incidence in the clinical diagnosis of polycystic kidneys in 3 large collective series is given in Table 1.

TABLE 1

The age incidence in the clinical diagnosis of polycystic kidneys in 3 large collective series.

Age, years	still-born	0–5	5–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90
Author											
KÜSTER	59	16	1	4	22	24	53	41	10	6	3
RALL and ODEL		5	1	2	18	70	56	41	13		
FERGUSSON		3	1			11	9	5			
Total	59	24	3	6	40	105	118	87	23	6	3
Per cent	12	6	3/4	1.5	10	25	28	21.5	5	1.5	3/4

The table shows that the disease has 2 pronounced maxima, one during the neonatal period, the other in adults at ages from 30 to 60 years. However, the disease occurs, although with a low incidence, in all age-groups between these two maxima.

Case report

Record No. 395/52. Pediatric Department of Sundby Hospital, Copenhagen. The patient is a girl, now 5 years old. She was born at term by normal delivery. Weight at birth 3900 g, length 52 cm. She was the second of 2 siblings. The elder brother and both parents were in good health.

She was first admitted to the department when she was 8 days old for gastro-enteritis acuta c. intox. She was discharged completely recovered after 6 weeks' stay in the department.

She was then in good health and was thriving until, at the age of 5 months, she was readmitted owing to fever and foetid urine. Enlargement of both kidneys was then ascertained, described as the size of green walnuts, firm and smooth. The urine contained nothing pathological; microscopic examination of catheter urine showed nothing abnormal, and cultures from the urine were sterile. Repeated intravenous pyelography showed enlargement of both renal shadows corresponding to the findings on palpation, but it was not possible to see the calyces or the pelves. Direct pyelography showed in both sides a large, grossly dilated pelvis with large, dilated calyces. The left ureter passed medially to the center of the pelvis with a peculiar rectangular kink, whereas the course of the right ureter was normal.

During the patient's stay in the department for 18 months she had intermittent fever, the cause of which was not fully elucidated from the onset, for in spite of repeated examinations it was not until she had been in the department for 5 months that a growth of bacteria was found in the urine (Escherichia coli, enterococci and Proteus).

It was possible to combat this infection of the urinary tract with Lucosil, penicillin and streptomycin after determination of the sensitivity of the organisms; there were, however, frequent febrile recurrences caused by a changing bacterial flora.

During this period the patient developed a moderate anaemia (Hgb. 75 per cent), was tired, languid, without appetite, and was not thriving. She had hyposthenuria, and the blood urea level was elevated (maximum 55 mg %).

No diagnosis could be established with certainty in the department. The presence of bilateral Wilms tumours was considered out of the question, as the kidneys after observation for 18 months had not increased very much in size, apart from what could be expected according to the patient's age, and as the clinical course did not otherwise correspond to the usual findings in this disease.

The differential diagnosis lay between (1) hydronephrosis and (2) polycystic kidney. The peculiar kink on the left ureter at its origin from the pelvis (caused by aberrant vessels) and the dilated pelvis and calyces might weigh in favour of the former diagnosis. Polycystic kidney fitted in well with the clinical picture, but the pyelogram was not sufficiently characteristic to clinch the diagnosis.

For diagnostic reasons the patient was then subjected to an explorative kidney operation which was performed at Dronning Louises Børnehospital when the patient had just completed her second year.

Description of operation.—The left kidney was found to be the size of a fist or more, very nodular, of a red-brown colour, and in parts had bluish, translucent, cyst-like areas. The ureter was normal. The changes involved the whole kidney.

Biopsy.—The glomeruli were of a fairly normal nature, although in parts with a thickened Bowman's capsule; hyalinization or crescent formations were not b-

served. In a few areas both the convoluted and the collecting tubules showed some tendency to dilatation, but the epithelial lining was normal, and very few casts were seen. In some areas of the interstitial tissue there was a high degree of round-cell infiltration and some connective-tissue proliferation. In addition, numerous cystic cavities were found, lined chiefly with low, cuboidal epithelium; a few contained some crystalline, tabular deposits. There were no signs of acute inflammatory changes or of tumour formation. Diagnosis: cystes renum multiplex (polycystic kidney), nephritis chronica interstitialis in primis exsudativa.

The postoperative course was uneventful. Owing to the infection of the urinary tract (gram-negative, non-lactose fermenting rods) she was treated, after determination of the sensitivity of the organisms, with sulphathiazole and penicillin, with success.

In the course of the next 2 years she was admitted four times. The first two admissions took place owing to catarrhal affections and fever of very short duration. Examination of the urine showed normal conditions. On the third occasion she was admitted for direct pyelography. Urinolysis was normal during this stay in the department. Immediately after discharge she became ill with fluctuating fever and pronounced tenderness in both renal regions. This time a culture of Proteus was obtained from the urine. After treatment with Chloromycetin, and later Gantrisin, the temperature soon became normal, the tenderness in the lumbar regions was obviated, and the patient was feeling well. She has now been entirely free from these attacks during the past 18 months.

Somatically and psychically the patient has developed normally during this period and, apart from transient catarrhal affections, measles, chickenpox and bilateral otitis, treated with penicillin in her home, she has been in completely good health.

The only striking symptom which the patient presents now is a slightly increased thirst and output of urine.

Present state.—A 5-year-old girl. Psychically and somatically corresponding to her age. Hgb. 84 per cent. Micro-SR: 8 mm.

Physical examination showed nothing abnormal, apart from the findings on palpation of the abdomen where the kidneys are felt to be greater than the size of a fist and distinctly nodular. Catheter urine: no albumin, blood, pus or sugar. Microscopy of catheter urine: normal. Culture from catheter urine: sterile. The specific gravity of the urine varied from 1.006 to 1.012. The 24-hour output of urine was from 600 to 1.300 ml, most frequently 900 ml. Addis' test: maximal specific gravity 1.011. Urea clearance: I: 62 per cent, II: 92 per cent. Blood urea 33 mg %. Blood pressure: 135/80 mm Hg (previously: 130/80 — 155/110 — 160/110 — 140/90 mm Hg). Ophthalmological examination: no vascular changes. Roentgenologic examination of the heart: normal. Electrocardiogram: normal. Roentgenologic examination of bones: nothing abnormal. Serum calcium and serum phosphorus levels: normal.

Examination of the patient's family.—The writer examined the patient's father, aged 44, her mother, aged 40, and the brother, aged 10, for possible congenital polycystic kidney. The parents are not related.

Examination of the urinary tract, including indirect pyelography, showed normal conditions in all three persons. Further details were obtained about the parents' brothers and sisters, the grandparents and the great-grandparents. Nothing was found to support the assumption that polycystic kidneys occurred in the family. Death certificates and hospital case records for the dead relatives were examined. Even though it is known that the polycystic renal disease may take a course without

symptoms up to a comparatively advanced age, it was to be expected that pyelography would reveal the disease in the patient's parents.

Heredity.—It appears from the above that the congenital polycystic kidney in this patient occurred as an apparently isolated phenomenon in a family in which 4 previous generations have been investigated.

It is therefore improbable that the congenital polycystic kidney of this patient can belong to the dominantly hereditary type of the disease. When the hereditary classification established by WERNER is used, the patient's disease must be considered either as the result of recessive inheritance or as being of non-hereditary causation.

Diagnosis.—From the onset of the disease the patient presented the most decisive symptom of congenital polycystic kidney: bilateral enlargement of the kidneys.

During the early course the kidneys were felt to be firm and smooth, and it was not until a couple of years later that the typically nodular surface was palpated.

The indirect pyelography was of slight value as a diagnostic aid. The direct pyelography did not afford the diagnosis directly either, even though it revealed highly dilated pelves and calyces and a distinct medial dislocation of the left ureter at its origin from the pelvis.

The diagnosis was not definitely established until explorative operation was done. The macroscopic and microscopic pictures of the kidney closely corresponded to the type of polycystic kidney seen in adults and in children beyond the neonatal period.

The clinical course was characterized by the recurrent infection of the urinary tract with high fever, bacilluria and pyuria, and, on one occasion, pain in the renal region. The patient had never had haematuria. After treatment with the modern sulphonamides and antibiotics she has now been free from these attacks for 18 months. The renal function is slightly decreased, with isosthenuria, slight polyuria and resulting polydipsia, whereas the urea clearance is hardly decreased. She has a slight arterial hypertension without cardiac or retinal changes.

Prognostic deliberations.—It must be assumed that the patient's future will first and foremost be threatened by the following two complications: (1) Recurrent infection of the urinary tract, and (2) progressive renal insufficiency with increasing arterial hypertension. With regard to recurrent infections of the urinary tract, we are today so well equipped with diagnostic aids and means of effective treatment that it should be possible to control these infections to a great extent. It must be taken for granted

TABLE 2

Survival time and cause of death in 9 reported cases of polycystic kidneys.

Author	Sex	Age when diagnosed	Symptoms	Age at death	Cause of death	Polycystic kidneys in the family
KRETSCHMER	♂	5 months	pronounced rachitis, bilat. renal tumour, isosthenuria, hypertension	4 yrs.	uraemia	none
GREEN	♀	8 months	pronounced rachitis, albuminuria, hyposthenuria	3½ yrs.	uraemia	none
ROYSTER	♂	4 weeks	not thriving, bilat. renal tumour	8 months	uraemia	none
PARROTT	♀	11 weeks	hypertension, left-sided cardiac hypertrophy	11 weeks	uraemia	none
SMITH and GRAHAM	♀	8 yrs.	severe anaemia, albuminuria, isosthenuria	8 yrs.	uraemia	none
GLASER	♂	22 months	recurrent pyuria	22 months	uraemia	none
ROSSEN	♀	9 yrs.	recurrent pyuria	14 yrs.	uraemia	none
CUMMING	♂	6 yrs.	albuminuria, hypertension	14 yrs.	uraemia	none
WILLAN	♀	palpable renal tumour when few months old	17 yrs. old, symptoms?	31 yrs.	uraemia	none

that a rational counteracting of the infection of the urinary tract in polycystic kidney will lead to an improved prognosis of this disease, although this has not yet been substantiated in the literature. Even though it is possible to keep the patient free from infection of the urinary tract, her future existence will be threatened by an increasing renal insufficiency which is likely to develop in comparatively few years. A survey of the survival time in the few cases of polycystic kidney in children giving rise to symptoms that have been reported in the literature is shown in Table 2.

It appears from the table that the duration of life, reckoned from the age when the diagnosis was established, has varied from 4 to 8 years. A case of polycystic kidney in a woman reported by WILLAN is an excep-

tion: when she was a few months old, a tumour of the kidney was diagnosed, at the age of 17 she developed symptoms, and when 31 years old she died in uraemia. In the extensive literature on polycystic kidney the writer has found 7 dominantly inherited cases in children aged 2 to 13 years; here the disease had occurred in from one to several generations, but none of these had been followed till death in uraemia. Finally, some cases of polycystic kidney have been reported in children who died of intercurrent diseases and in whom the polycystic kidney disease was a chance finding.

Therapy

With regard to therapy in cases of polycystic kidney, all authors agree that this should be medicinal, and that surgical treatment should be conservative and palliative.

The medicinal treatment is similar to that in nephritis. As polycystic kidneys are often infected, chemotherapy is of great importance in the treatment of this disorder, and will often be able to prevent pyelonephritis and abscess formation which was previously a common and severe complication.

Surgical therapy is used primarily in order to (i) obviate pain in the lumbar region, (ii) check fatal haemorrhage, and (iii) remove abscesses or calculi. Further, as stated by some authors, it is used in cases with rapidly decreasing renal function; for when the pressure on the inhibited renal tissue still capable of function is relieved, the renal function improves temporarily.

The surgical treatment in the method described by ROVSING in 1911 involves puncture of as many of the cysts as possible after the kidneys have been exposed. However, the cysts are fairly soon re-formed. ROVSING's operation has therefore been extended, as a sclerosing substance is now injected after puncture in order to prevent re-formation of the cysts. The various authors have used different sclerosing substances ("Varicocide", 50 per cent solution of dextrose, quinine hydrochloride and -dihydrochloride). The mortality in puncture treatment of cysts has been stated to be 13–16 per cent in two series of 29 and 23 cases respectively.

Other surgical interventions which may be considered are drainage, nephrostomy and nephrolithotomy. The mortality in nephrostomy has been stated to be 29–45 per cent in two series of 21 and 27 cases respectively.

All authors agree that the surgeon should hesitate to do a nephrectomy, and state that this operation should only be performed in cases with persisting suppuration or haematuria where other therapy has failed, and in case of malignant tumour in the cystic kidney. The mortality in this operation is high, about 30 per cent, and an apparently healthy kidney often develops large cysts in the course of 1 to 3 years after contralateral nephrectomy.

No studies have been published on prophylactic surgical operations in early diagnosed, apparently symptomless cases, and it was therefore considered that no form of surgical therapy was indicated in the present case.

Summary

The writer reports a case of bilateral congenital polycystic kidney in a girl who is now 5 years old and who has been followed from the age of 6 months. The diagnosis was established by explorative operation and verified by tissue microscopy. The disease appeared as bilateral enlargement of the kidneys and recurrent febrile infections of the urinary tract during the first two years of life. These were combated with sulphonamides and antibiotics. During the past 18 months there has been no infection of the urinary tract. Both somatically and psychically the patient has developed normally, but now presents isosthenuria and slight arterial hypertension. There have been no cases of polycystic kidney in the family.

Un cas de rein polycystique congénital chez un enfant.

L'auteur décrit un cas de rein polycystique bilatéral congénital chez une fillette, qui est actuellement âgée de cinq ans et qui a été suivie depuis l'âge de six mois. Le diagnostic a été fait après opération exploratrice et a été confirmé par l'examen microscopique. La maladie se manifesta par une augmentation de volume des deux reins et des infections répétées des voies urinaires avec fièvre élevée pendant les deux premières années de la vie. Celles-ci furent combattues par les sulfamides et les antibiotiques. Il n'y eut plus d'infection de l'appareil urinaire pendant les 18 derniers mois. L'enfant s'est développé normalement tant du point de vue psychique que somatique. Elle présente cependant maintenant une isosthénurie et une hypertension artérielle légère. Il n'y a pas eu de cas de rein polycystique dans la famille.

Ein Fall von angeborener polycystischer Niere bei einem Kinde.

Verf. berichtet über einen Fall angeborener, beidseitiger, mehrfacher Cystenniere bei einem Mädchen, das nunmehr 5 Jahre alt ist, und das seit dem Alter von 6 Monaten klinisch verfolgt werden konnte. Die Diagnose wurde durch eine explorative Operation gestellt und durch mikroskopische Untersuchung verifiziert. Die Krankheit trat zutage durch beidseitige Vergrösserung der Nieren und recidivierende hochfebrile Infekte der Harnwege während der ersten zwei Lebensjahre. Sie konnten durch Sulfonamide und Antibiotica beseitigt werden. Während der letzten 18 Monate ist keine Reinfektion der Harnwege aufgetreten. Pat. entwickelte sich bisher sowohl körperlich als psychisch normal, zeigt aber jetzt eine Isosthenurie und leichte arterielle Hypertension. In der Familie konnten keine weiteren Fälle von polycystischer Niere gefunden werden.

Un caso de riñon poliquístico congénito bilateral en una niña.

El autor presenta un caso de riñon poliquístico congénito bilateral en una niña que tiene actualmente 5 años de edad y que ha sido seguida desde la edad de 6 meses. El diagnóstico fué establecido por exploración quirúrgica y verificato por estudio microscópico. La enfermedad apareció bajo forma de agrandamiento bilateral de los

riñones e infecciones recurrentes del tracto urinario acompañadas de fiebre alta, durante los dos primeros años de vida. Estos episodios fueron tratados con sulfonamidas y antibióticos. Durante los últimos 18 meses no han habido infecciones en el tracto urinario. Somáticamente y psiquicamente la paciente se ha desarrollado normalmente, pero ahora presenta isostenuria y ligera hipertensión arterial. No han habido casos de riñon poliquístico en la familia.

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COMMENTS

Consequences of Modern Trends in Pediatrics

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There has been recently a combined conference of the World Health Organization which brought together pediatricians, child psychiatrists and psychologists. This is the first meeting of its kind and it is a welcome subject for reflection and meditation. It implies the development of certain modern trends.

What are those trends? What are their chances, what their realms, their implications, their consequences? I have been thinking about this and would like to impart my views.

It may be wise to look back and see what happened to other trends which were modern in their time, for example biochemistry. To-day biochemistry has become a natural and essential part of pediatrics. It is likely that in the same way the time has come for psychology and psychiatry to penetrate pediatrics. More or less concurrently with this growing symbiosis two other basic lines of thought are being introduced into pediatrics; firstly the importance of growth and development of the normal child, and secondly the environment–child relation or the sociological aspect.

If those three trends, (1) psychology, (2) growth and development, (3) sociology, continue to grow in importance, this would imply drastic consequences in the following aspects:

1. The Pediatric Attitude of Mind

At the moment the average pediatrician is a physician who treats a disease of a patient. He may become a man who considers his patient as a socio-psycho-somatic entity, and he may be aware of the fact that disease is only a clinically observable deviation of normality.

2. Child Health

Child health and pediatrics will become more intimately related. Modern child health includes the study of environmental influences on infantile development. Such studies can be carried out on *groups* of children. The

concept of child health moreover stimulates the application of measures for prevention of disease and for promotion of health in *all* children. Here the sociological aspect, the environment–child relation is paving its way.

3. *Nursing*

The old system in which one nurse took care of all the needs of one patient was discarded many years ago in favour of the prevailing custom in which the care for a patient is divided into various specialized duties, which are performed by different nurses. To-day the better understanding of interhuman relations makes it clear that this situation considerably increases the feeling of insecurity in the child. Not only is this way of working detrimental to the child; it also gives little satisfaction to the nurse. For these reasons the question arises whether it would not be preferable to organize the nurses into teams composed of a specified number of nurses who work together as one unit. Each of these units would be solely responsible for the care and needs of one particular group of children. Another important point in the nursing situation deserves consideration. The nurse spends all her time on the patient, the doctor not more than a few minutes, in which he pays more attention to medical data than to the patient himself. Therefore the average nurse will observe many things about her patient, of which the doctor cannot be aware. Exceptionally few doctors grasp the advantages of this situation. It is the common thing for doctors to regard a nurse as someone who simply has to be there.

4. *Hospital Building*

Several factors may influence modern hospital building, for example the above-mentioned nursing teams. The introduction of nursing teams implies that one team can serve only a limited number of patients. This may well influence the size of wards and the grouping of cubicles. In addition, during the last few years it has proved desirable in the Western world to hospitalize, in some cases, the mother together with the child. And already the opinion is breaking through that hospitalization of children below the age of 6 should be restricted to those cases which cannot be treated at home in any possible way. Then there is a trend to extend visiting hours on a psychological basis. Such factors may well necessitate a revision of hospital building. The outpatient department might be changed so that large waiting-rooms become superfluous—partly because these rooms increase the chances for infections of the children and the anxiety of the mothers, and partly because an appointment system is more economical.

5. *Staff.*

The hospital staff should be composed in such a way that adequate care for the patient can be given in psychological and sociological respects so that the normal psychological development of the child in hospital can continue, instead of being interrupted as is now often the case in chronic patients. Once the patient has left the hospital after-care seems to become inevitable in order to prevent that the result of hospitalisation is neutralised in a short time. This too requires staff.

6. *Research.*

One might still get the impression that the prevailing opinion of true scientific research means predominantly biochemical and pathological research. But already the signs of our changing attitude are recognizable and research work in the surrounding psychological, sociological and embryological fields is gaining importance and mingling with pediatric research.

7. *Teaching.*

Teaching is my last point. Perhaps it is the most important one because it guarantees the continuity and standard of our specialty. Teaching in my days was far from ideal, and as it has not changed much I gather that it is not ideal even now. One could look upon teaching in three different respects, (a) *subject*, (b) *method*, (c) *the teacher himself.*

(a) *Subject.*—With our changing views as regards the importance of psychology, growth and development and sociology, it seems advisable to incorporate these into the curriculum.

b) *Method.*—As a rule the medical student is overloaded with a number of lectures the contents of which nobody could possibly digest. The way of lecturing nearly always is such that only the teacher plays an active role, whereas the student is passive. This, as we pediatricians know more than anyone else, is contrary to the condition in which a human individual learns optimally. The atmosphere of the lecture room is one of insecurity for the student, which certainly will not facilitate his learning capacities. It is clear that this situation has to be changed completely. We who live on the European Continent may learn in this respect from our American colleagues. We may say that lectures should be given less frequently. A more active attitude of the student may possibly be achieved in group discussions. And there should be no feelings of insecurity or anxiety in the student-teacher relationship. Certainly this will require a much more complex teaching staff.

c) *Teacher.*—In order to promote the condition in which the human being feels secure and learns favourably, the ideal teacher should possess the following qualities: (i) he should love his students; (ii) he should be capable of understanding them; (iii) he should be patient; (iv) he should be a good listener; (v) he should be a good narrator; (vi) he should like and know his subject.

If a teacher possesses these qualities one may expect that his students will feel at ease and be keen and active. Therefore it seems highly desirable that more attention be paid to those qualities, and that every teacher should try to develop them.

I will restrict myself to these seven points: *pediatric attitude of mind, child health, nursing, hospital building, staff, research, and teaching.* Today these seven points are more or less desiderata, but to-morrow they may be realities. As such they will determine the atmosphere of our pediatric education. They therefore require and deserve full consideration.

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Proceedings of the Pediatric Society of South Sweden

Meeting, Växiö, October 24, 1954

I. Nilsby: **Sequelae of meningo-encephalitis.**

Meningo-encephalitis is a common disease in children, often overlooked or incorrectly diagnosed because the symptoms are frequently mild or uncharacteristic. Most common are the so-called secondary meningo-encephalitides after various child diseases, such as morbilli, varicella, parotitis, but also following other infections such as rhinopharyngitis, dyspepsia and after smallpox vaccination. In the majority of cases cure is accomplished without sequelae. In the cases where after-effects are encountered they can be either neurologic (pyramidal or extrapyramidal (motor disturbances, together with convulsions) or psychic unstability, impulseness, abnormal exhaustion and difficulty in concentration). The intelligence, as a rule, is not reduced, but some partial functions, such as form-conception and the ability to integrate different perceptions, are often effected. This, along with the psychic symptoms, frequently causes school difficulties in these children.

S.-I. Björklund: **Hemihypertrophy and Wilms' tumor.**

(Will be published in Acta Pædiatrica 44, 1955.)

R. Thelin: **Splenectomized case of hypersplenic anemia.**

A boy, at present 3 years old, developed increasing icterus 6 hours after birth. The mother was found to be Rh-negative and iso-immunized. Two siblings, 18 and 15 years old, are in good health. The patient was Rh-positive, group A. An exchange transfusion was performed with Rh-negative group A blood: 350 ml were drawn and 400 ml were administered. Thereafter, the blood values steadily decreased so that the patient had to be given transfusions at regular intervals; a total of 40 in 2 years. The curative effect has been negligible, as was also the case with drug therapy (iron, cobalt, copper, liver preparations and cortisone). The white blood cell picture, thrombocytes, osmotic resistance, bleeding and coagulation times have been normal. The activity of the bone marrow has been rather good. Reticulocytes range around 20 per cent with a maximum of 70 per cent on one occasion. The spleen has been enlarged from 3 months of age. At 9 months the patient was found to be Rh-negative, after previously having been positive. The samples were taken 6 weeks after the last transfusion. Repeated controls have since been carried out with the same result. Splenectomy was performed at 2 years of age. The patho-anatomic diagnosis revealed pronounced hemosiderosis, slight fibrosis of the pulp and no hyperplasia of the endothelial sinuses. Blood values have been normal ever since the operation (the last samples were taken 1 year after the operation).

R. Jönsson: **Neurogenic laryngeal stridor.**

A 6-month-old boy has been hospitalized in the Pediatric Department since 2 months of age for stridor and attacks of apnea, cyanosis and loss of consciousness. The stridor is of both the inspiratory and expiratory type and occurs almost always while the patient is awake. The attacks take place a few minutes after the completion of a meal. They begin with the patient becoming restless; the stridor increases, whereupon he suddenly becomes pale with cyanosis and loss of consciousness. He lies in this condition for a few minutes up to 10 minutes, during which he draws a few breaths and finally awakens and begins to scream. Blood chemistry and roentgenograms of the lungs and heart, trachea together with the esophagus and ventricle reveal normal findings, just as electrocardiograms during free intervals. Electroencephalograms were normal. Laryngoscopy yields a normal picture. Electrocardiograms taken during attacks show bradycardia, about 50/min, and a total suppression of the sinus node with transference of the impulse formation to the lower part of the A–V node. The patient was improved on phenantoin and further improved on a large dose of atropine.

Similar cases have recently been described (ALLEN *et al.*: Am. J. Dis. Child. *87*: 179, 1954). The attacks are probably released over a vagovagal reflex with an afferent path from a "trigger zone" in the upper part of the gastro-intestinal tract. The impulses reach the vagus motor center, via reflex paths in the central nervous system. The vagus motor center gives efferent impulses to the heart with suppression of the sinus function and a corresponding effect on the respiratory frequency producing laryngeal stridor. The loss of consciousness is probably a secondary phenomenon. Phenantoin is believed to break the cerebral reflex path and the atropine the peripheral link in the chain. The prognosis is probably good.

Section of Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, December 5, 1954

Symposium on rickets.

B. Bille: **The diagnosis of rickets, especially with regard to non-rachitic craniotabes.**

(To be published in *Nord. Med.* 1955.)

J. Winberg: **The incidence of rickets in Sweden.**

An attempt is made to evaluate the presence and distribution of rickets by analysis of rachitic cases, collected from various children's clinics over the whole country. During the years 1944 to 1953 about two hundred to three hundred cases have been reported anually. In 1944, the number of cases of rickets in one hundred hospitalized children was 1.55 and the corresponding figure in 1953 was 0.55. This decreasing tendency probably depends upon a decreasing birth rate, more intensive investigations by the Children's Welfare Centers, and the more rigid diagnostic criteria. The difference in frequency of rickets among hospitalized children in the Northern and Southern districts is astonishingly small. Sixty-five per cent of 2,530 cases of rickets were

boys. The sex difference was greatest in the younger age groups. Vitamin D intoxication with typical clinical symptoms and cases of primary vitamin D refractory rickets seem to be very uncommon.

Olof Mellander (Guest): **The need of vitamin D in growing individuals.**

There is no sure ground for evaluation of the need of vitamin D in the growing child. The need varies with the fat absorption and with the form in which calcium and phosphorus are supplied to the organism. An interaction between protein and mineral metabolism occurs, the breast-milk protein produces higher molecular peptides during digestion than the cow's milk protein and these peptides promote absorption of the minerals. The need of vitamin D therefore is lower in breastfeeding. Laboratory animals on a vitamin D deficient diet can be protected against rickets by a supply of such peptides. In certain cases, especially in England, there has been a pronounced hypercalcemia associated with renal lesions which has been supposed to be due to a vitamin D intoxication, although the supply of vitamin D in several cases has not surpassed 2,000 U. per day. It has been maintained that these cases have a very strong sensitivity to vitamin D. Milder degrees of such conditions probably occur but are difficult to diagnose. The supply of vitamin D should therefore not surpass 800 U. daily. The vitamination of milk products with vitamin D implies risk for hypervitaminosis by the double prophylaxis that may occur in such cases.

Gert von Sydow: **The desirability of uniform principles in the prophylaxis of rickets.**

The prophylaxis of rickets should be started before disturbances in the mineralization occur that may lead to rickets. The expectant mother, therefore, should be given vitamin D. The postnatal prophylaxis against rickets should be started during the first few weeks of life, in breastfed as well as in artificially fed babies. The vitamin prophylaxis is recommended to start in the Northern part of Sweden in the first two weeks of September and to continue until Midsummer. In other parts of Sweden, from the 1st of October until the 31st of May. Infants born after January 1 should get vitamin D prophylaxis even during summertime. The prophylactic dose of 300 to 400 U. recommended by Jeans and Stearns does not suffice to protect children that are especially sensitive to rickets and is therefore not adequate as mass prophylaxis. A routine dose of 2,000 U. daily is therefore recommended for infants in "Norrland" and 1,500 U. daily for infants in other parts of Sweden. These doses correspond to 15 and 10 "AD-vitamin drops" respectively. After infancy there is no reason to give such high doses. For children between 1 and 7 years of age, a dose of about 750 U. is recommended, corresponding to 5 "AD-vitamin drops" daily. In long-lasting infections this dose should be doubled. To all children and growing adolescents the same dose is recommended during the dark season.

Discussion: *Sven Kraepelien*: Several eczematous children and even other types of allergic children react unsatisfactorily to the native D-vitamin compounds and because this group is not a small one it is suggested that synthetic D-vitamin preparations should generally be recommended instead of the native preparations now commonly used. What this entails from an economical point of view cannot be discussed here but will be postponed to later publication.

Bo Vahlquist: **Continued experience with triple-vaccination.**

Triple-vaccination against whooping-cough, diphtheria and tetanus are used with increasing frequency in Sweden. The effect of the vaccination must be regarded as very

good. Studies by Melander-Vahlquist and collaborators on 100 to 150 children have shown that three injections of 1 ml of the Swedish vaccine at the ages 3 to 6 months give titres of diphtheria-antitoxin identical with, or above, 0.10 A.U. in 90 per cent and whooping-cough agglutinin-titres corresponding, or above, 1:320 in 95 per cent of the cases. In Uppsala, triple-vaccination during the last few years has been given to about 70–80 per cent of infants. In 78 children, 0–4 years of age, who were ill with whooping-cough, 4 per cent had been vaccinated. Of 59 unvaccinated siblings to children with whooping-cough 52 (= 88 per cent) contracted the disease. Out of 9 completely vaccinated, only 3 fell ill, and all these cases were very mild.

Bengt Karlsson: **Poisoning and threatening poisoning in infants.**

At the Crown Princess Lovisa Children's Hospital in Stockholm 3,185 accidental intoxications or possible intoxications have been admitted between 1945 and 1953. Ninety-five per cent of the poisonings have occurred before five years of age, most of them during the second year of life, especially the first half of it. Out of the total number of cases the boys constitute 56.8 per cent. Ten per cent of the cases were seen before one year of age. In this group, the boys constitute 35.4 per cent. The number of poisonings shows an increase from 1945 to a maximum in 1951, and thereafter a tendency to decrease. The increase is due to an increase in the use of the groups of drugs, technical compounds and tobacco in about the same relationship. Tobacco is the most frequent of the intoxications (27 per cent). Commercial substances comprise 25 per cent and drugs 23 per cent. Cleaning compounds are most frequent among the technical substances, and sedatives, cough medicaments and laxatives among the remedies. Out of the whole group of possible poisonings, 14 per cent have shown signs of intoxication and 4 of these children died. Considered as highly potential risks of poisoning are sedatives, cough medicines, iron-tablets, some cleaning fluids and analine-containing ink, and certain insecticides. The difficulty in identifying the causes of intoxication makes a continuous central registration of toxic preparations from the technical industry desirable. The risk of gastric lavage is stressed. According to experiments with animals, there are certain indications that gastric lavage gives rise to alarming symptoms. From a prohylactic point of view especially improved means of protection are desirable. Thirty-four per cent of the cases of poisonings belong to social group 1; of the total population of Stockholm 11 per cent belong to this group.

Discussion: *Kristiansson*. Demonstration of a specially constructed cover for bottles containing drugs. In order to remove the cover a combined movement of pressure and screwing is necessary, which in addition requires a certain force. This cover has been tried with more than 300 children aged 1 to 12 years and has proved to fulfill the demands for safety. The solidity of the cover is satisfactory.

P. Karlberg, S. Iggbom and A. Perman: **A diagram for evaluation of the growth of Swedish children.**

In this diagram the height was put in relation to age, and the bodyweight in relation to the height of the child. Logarithmic scales were used in order to have all the ages from one month to 16 years on the same diagram and also in order to visualize percentile deviations from the mean values in all age groups. The variations for these two relationships in the two examined groups, on which the diagram was drawn, has been given in ± 2 sigma, that is in 95 per cent confidence interval. The diagram has been

used at the Pediatric Clinic of Karolinska Sjukhuset for several years and has proved to be of great value.

Discussion: *Bengt Jonsson*: Development diagrams of the type that Karlberg has demonstrated are of great value also in determining whether a group of diseases deviates from the normal distribution. If a large number of such cases are put into the diagram it is easy to see if there is any deviation. — *C. G. Bergstrand*: If one wants to follow the growth in a case of developmental deficiency and to compare it with normal conditions, the values seen in the older age groups are so compressed that visiability suffers. — *Carl Grünewald*: It would have been better if this diagram had not been based only on children from Stockholm. There is reason to believe that the curve of growth should show a peak corresponding to fat children and an oblique distribution that probably is more pronounced for instance in children from the South of Sweden. The practicability of the diagram should also be increased if lines corresponding to one or one and one-half sigma were drawn, recording the per cent figures that these values represent.

***Bengt Jonsson and Petter Karlberg*: Open oxygen box according to Batson.**

Short demonstration of an oxygen box. The box is made by plastic and has bottom and walls but no roof. The oxygen has to pass an ice container where the oxygen is cooled down and is introduced at the bottom of the box. The cool oxygen remains at the bottom of the box while the warm expired air moves upwards (that is, out into the room). With an oxygen flow of 7–8 liter per minute, an oxygen concentration of 50–60 per cent is attained at the nose of the child, and the temperature is 15–16° C. An apparatus combined with refrigeration has been constructed but has not yet been tried.

***F. J. Stare, Boston* (Guest): Teaching of nutrition in the medical curriculum.**

Research and teaching of nutritive problems has long been a neglected part of medicine, and still the composition of our food is surely the most important factor in the preservation of our health. The teaching of nutrition must, therefore, constitute a part of the curriculum of every medical school. In order to do this teaching in a satisfactory way a professor of nutrition should be appointed to each university. This professor should be responsible for the general lines of teaching. He is, however, as a rule, a biochemist and is not prepared to do clinical teaching. He should, instead, give impulses to and stimulate clinical teachers; everyone of them should have the responsibility of teaching nutrition to students. Nutritional teaching has followed these lines in Boston and has functioned to the satisfaction of all concerned.

Discussion: *Bo Vahlquist*: I think we all agree that Doctor Stare has given us a very interesting lecture on an important subject. Pediatricians should be especially inclined to listen carefully. Since times long past the nutrition of infants has been a major problem. Furthermore nutrition is a major part of preventive medicine, and pediatricians have always had their eyes open in this field. It would be progressive if some kind of position for research workers in nutrition could be founded at Swedish universities.

***G. Ekström, H. Lundberg and T. Möller*: A follow-up study of surgically treated pulmonary stenosis.**

Sixty-nine cases of pulmonary stenosis, isolated or combined with a septal defect, have been diagnosed at the Crown Princess Lovisa Children's Hospital. Sixteen of them have been operated, all of them by transventricular valvulotomy according to

Brock. The mortality has been nil. In 5 cases, continuous measuring of the pressure in the pulmonary artery and right ventricle has been done during operation. These measurements have shown that the pressure in the right ventricle decreases before the beginning of the valvulotomy and increases again after narcosis. Isolated measurements of the pressure by heart puncture could give misleading results regarding the effect of valvulotomy. Follow-up studies have shown a good result of the intervention. The observation-time has varied between three weeks and three years. All the cases have reported improved physical ability. Ten cases have been catheterized after operation. There was a decrease of the pressure in the right ventricle, as a rule to about 50 per cent of the value before operation. One case showed a decrease of the pressure that was not satisfactory. The peripheral arterial oxygen tension, in cases combined with septal defect, has been improved after operation. In all cases with a long observation-time the hypertrophy of the right ventricle has diminished. Roentgen examination of the heart showed very minute changes after operation.

Discussion: *Bengt Jonsson*: In left to right shunt with increased flow through the pulmonary ostium one can get a pressure gradient between the right ventricle and the pulmonary artery depending upon the effect of the rapidity-pressure, without the existence of an anatomical stenosis. We have found a gradient up to 20 mm Hg without anatomical stenosis. The effect of valvulotomy has often been ineffective. It is possible that there is only a dilatation of the membrane. An effective resection can certainly be done without risk. The pulmonary deficiency that occurs in such cases does not constitute disadvantageous risks because the diastolic pressure in the pulmonary artery is so low that no regurgitation of importance can develop. — *E. Mannheimer*: Pulmonary stenosis combined with atrial septal defect should be operated. One should be careful, however, when there is a question of pulmonary stenosis combined with ventricular septal defect and an important left/right shunt. From a hemodynamic point of view these latter cases with right/left shunt are almost identical with cases of tetralogy of Fallot.

***Göran Sterner*: Primary atypical pneumonia.**

Between 1945 and 1953, 118 cases of primary virus pneumonia were admitted to the four children's hospitals and the Hospital for Epidemic Diseases in Stockholm. The highest number of admissions were during Oct., Nov., Dec., 1953, and Jan. 1954. During the same period more cases of virus pneumonia have been treated at the children's departments of Sundsvall, Falun, Västerås, Örebro and Norrköping than ever before. The youngest of the 118 children was 10 days and the oldest 15 years, most of the children belonging to the group, 8–12 years of age. The incubation period was 14–21 days. Contact cases could be traced in 32 per cent. The symptomatology corresponded to previous observations. There were very slight physical pulmonary findings in 38 cases and normal findings in 14 cases. The most dominant sign was consonant râles. The roentgen picture of the lungs showed homogeneous unsharp infiltrations. The white corpuscles varied between 3,200 and 21,2000; only four children had counts over 13,000. There was a normal or a slight shift to the left of the white cells. The sedimentation rate was usually very high. The cold agglutination test in 115 cases was in 74 per cent 1:32 or higher. In cases treated with a tetracycline type of antibiotic the temperature was normalized a little earlier than in untreated cases, but the roentgenological lesions remained as long in these cases as in the untreated ones. The complications were very few (mild otitis, sinusitis, nephritis and meningoencephalitis). Three children died aged 10 days to 1 year. In these 3 cases interstitial

pneumonia could be demonstrated post mortem. In the infants, there were no plasma cell elements.

Discussion: *K. Kaiser*: During the Autumn 1954, several cases of persistent bronchitis with severe cough and mild fever were observed at Eskilstuna. The occurrence among children that previously had had whooping-cough and the lack of leukocytosis speak against whooping-cough. K. is inclined to regard this bronchitis as due to virus infection. There were no roentgenological parenchymatous changes. The conception of primary atypical pneumonia probably contains several different kinds of virus infection. Similarly it is probably also that so-called virus bronchitis may have a variable etiology.

L. E. Carlgren and G. Nathorst-Windahl (Guest): **Interstitial pneumonia, a disease of importance at institutions for infants.**

A small epidemic of interstitial pneumonia in an infants' home in Gothenburg is reported and a description of the symptomatology of the disease and its etiology is given, especially with regard to the possible pathogenic significance of the parasite, Pneumocystis carinii; this parasite was demonstrated in the reported cases.

Discussion: *B. Vahlquist*: It is remarkable that this disease is limited to premature infants only; one can discuss if the antibody situation is especially unfavourable in prematures, due to the low gamma-globulin content of the blood. Tobler reported (1950) that he had tried gamma-globulin prophylaxis on a big scale, but, unfortunately, without success. It is disquieting that the disease now occurs also in Sweden. — *E. Mannheimer*: Has hypothermia been tested? Hypothermia should diminish the need of oxygen and may be antiparasitic. — *L. E. Carlgren*: We have not tried hypothermia. Even if this treatment would seem to be indicated due to the air hunger, one knows fairly little about the effect on the parasites. It is at least possible that their vitality could be increased by low temperatures.

Elsa-Brita Nordlund: **Child-psychiatric consultant work in a pediatric clinic.**

At the Pediatric Clinic of Karolinska Sjukhuset 12,580 children were admitted between January 1, 1952 and December 1, 1954. Five hundred and twenty-three children (that is, 4 per cent of all) were transferred to the child psychiatrists for consultation. This figure is low, due to certain restrictions. The age groups are almost evenly distributed without any remarkable peaks. The preponderance of boys is unimportant. The following principles have been followed as guide for the referring pediatrician: (1) All cases in which a mental examination constitutes an important part of the diagnosis; (2) Children are admitted routinely, when they are suffering from diseases that are produced or influenced by mental factors (for instance in asthma, ulcerative colitis, adiposity, etc.); (3) Sensitive children suffering from somatic disease should be prepared for necessary painful examinations and treatments, operation, heart-examinations etc.; (4) All children, where the pediatric colleage desires help from a child psychiatrist, when there is a question of collaboration with the parents, with personnel of the hospital, etc. Every week there is a conference with discussion about the cases that have been sent for consultation. In this discussion, psychiatrists, psychologists, social workers and pediatricians take part and this is of importance for successful collaboration involving these branches.

Discussion: *E. Mannheimer*: It is difficult to determine which cases the pediatrician can treat himself and which cases should be sent for consultation. Each case

takes a very long time for the child psychiatrist and all cases shouldn't be sent. The waiting-time often is very long. — *E. B. Nordlund*: At the Karolinska Sjukhuset Child-psychiatric Department we are short of personnel and the consultant cases must be picked, but this is done after discussion with the pediatricians. We must also concentrate on the more urgent cases. I do not believe that we psychiatrists have any great anxiety that the pediatricians should impose upon our domain. Our mutual field of activity is sufficiently great and we are grateful for the stimuli that these collaborations give us.

Bertil Söderling: **Some considerations on the social adjustment of the child, with special reference to the personality of the pilferer.**

The child must be adjusted to the reality of the world that is ruled by adults, which a child is not yet capable of understanding. At a certain age the community demands such an adjustment. A social adjustment is the faculty to differentiate between "mine" and "thine". That is not a primary capacity of the child. Another adjustment is the concretion of phantasy life, and differentiation between imagination and reality. Lacking emotional contact during early childhood or suppressing the need of activity the child feels itself rejected and misunderstood. Human contact is replaced by dead things. A child with a rich imagination remains in the life of phantasy of lower development stages. In this unreal life the phantasy is filled by the wishes and needs of the child. Beside lacking emotional relationship to the parents there are also other factors, for instance physical and mental inferiority in relation to playmates. A child that is mentally retarded and fit to go to school in a help-class, should never attend a normal class. Lacking the possibility of keeping up with the standard, the child is prone to pilfer in order to uphold his position. The author mentions different types of pilferers and different forms of pilfering. Conclusion: A pilfering child must be regarded as deficient in its development and not as a criminal. Therapy must be directed according to this principle.

G. Rodhe: **The activity of the school health officer in the field of mental hygiene.**

When there is a question of children with difficulty at school, the school physician should not limit himself to a somatic examination in order to exclude physical causes to the psychical disturbance. Even without any training he must devote himself to these children and make an initial evaluation of the conditions. He can, by his work, be a mediator between the child, the parents and the teacher, and by his objective view of the situation can calm all interested parties. Psychosomatic disease are frequent among school-children and demand examination and study of the child's psychological situation. The schools have great difficulties to overcome: Reform-work, too few teachers, too big classes, lack of rooms, and duplicating of the classes. These inconveniences make the children suffer and make still more urgent the need of collaboration with the school physician in the mental hygienic field. This work takes a long time but the generally improved hygienic standard permits the devotion of more time to the mental hygiene programmes.

A. L. Bergström, I. Olow, B. Söderling and M. B. Gunther: **Developmental-psychologic studies on premature infants.**

Studies of the relationship between the underweight child's reflexology and its faculty to suck were carried out according to the schedule of Gesell in his book, "The

Embryology of Behavior". In routine examinations these tests are too subjective or impractical, and they were therefore eliminated from the final schedule of investigation. In this scheme, the performances at every test have been graduated. The examined group comprises 33 premature infants with birthweights between 1,160–2,490 g. No statistically significant conclusion can be drawn, but it would seem from the examinations that the maximal prehension and the abdominal position reflexes develop concomitantly with the faculty of the infant to suck ad limitum. These faculties are attained between 36–37 weeks of fetal life. If this relationship should prove, in the future, to be physiologic, one ought to suspect illness or malformation in children where there is a lacking correspondence between these factors. In addition one should be able to determine rather exactly the length of gestation by the performances of the child. Physiological criteria as a principle to evaluate prematurity instead of the hitherto accepted principle, the birthweight is an advantage.

I. Nylander: **Child-psychiatric viewpoints on the prognosis of encephalitis.**

Seventy-four clinically studied meningo-encephalitic cases have been followed up in order to study the postencephalitic symptoms and signs, especially with regard to hereditary and constitutional factors. In nine cases there was an invalidating emotional disturbance, coloured by anxiety and psychic stress phenomena. Marked hereditary charge, serious disturbances in the home surrounding and a premorbid personality with vulnerable psyche occurred in all these cases. In 30 cases there were milder mental symptoms without adjustment difficulties for the child. In 22 of these cases, hereditary charge or nervous signs was demonstrated in the child before the encephalitis. In 35 cases in which heredity, surrounding and premorbid constitution were normal, there were no postencephalitic symptoms. The incidence of obsession symptoms in the group studies is surprisingly high. It might be asked if children with a certain constitution (careful, anxious, unsure children) have greater tendency to react with serious mental postencephalitic symptoms than other children.

Discussion: *B. Hamne*: Coercive activity as a sign of cerebral lesion occurs also in petit mal. H. has seen a case of coercive laughing on this etiological basis, and one case in which the patient, a schoolboy, several times during each lecture plucked at his clothes and repeatedly swore. Both had electroencephalographic pathological tracings typical for petit mal, and they became free from their coercive activities after Tridione treatment. — *J. Ström*: The question of psychic disturbances and conditions of insufficiency after acute meningoencephalitis is of great importance. One should also put etiological stress on the problem. To treat serous meningoencephalitis as a clinically uniform complication to various virus diseases is erroneous. Already during the active stage the cases can be clinically differentiated in many respects and the consequences of the disease that can develop may probably vary as well.

Meeting, Dec. 6, 1954

D. Frederick Stare, **Prof. of Nutrition, Harvard School of Medicine, Boston: Current trends in Nutrition Research.**

In a general discussion dealing with recent trends in nutritional research, Dr. Stare stressed the consequent extension in scope of this field. As examples of developments with which he has dealt personally he discussed in greater detail his studies on the nutritional aspects of atherosclerosis in addition to recent experimental work dealing with obesity.

Discussion: *G. Nylin* asked if Dr. Stare considered the determination of serum β-lipoproteins to be of value in the diagnosis of myocardial infarction associated with atherosclerosis. — *F. Stare* stated that he felt that the serum β-lipoproteins were of no value in making such a diagnosis, but he hastened to stress the experimental importance of these determinations by the ultracentrifuge technique. — *C. Gyllenswärd* discussed the hereditary aspects of obesity and stressed that environmental factors, as manifest through individual social inheritance, often make it impossible to evaluate true hereditary factors.

ANNOUNCEMENTS

The Eighth International Congress of Pediatrics. As decided at the seventh International Congress of Pediatrics in Havanna 1953, the eighth International Congress of Pediatrics will be held in Copenhagen, Denmark in 1956. The Congress will be opened Sunday, July 22nd, and closed Friday, July 27th, 1956. It is planned to arrange a scientific and technical exhibition in connection with the Congress. Further information will be sent to the national pediatric associations and also published in Acta Pædiatrica and Helvetica Paediatrica Acta. President of the Congress is Professor P. Plum, address: Domus Medica, Kristianiagade, Copenhagen, Denmark.

The Second European Cardiological Congress will be held in Stockholm September 10–14, 1956. Pertinent information can be obtained from the General Secretary, Dr. Karl E. Grewin, Södersjukhuset, Stockholm.

The Fifteenth Congress of the Association des Pédiatres de Langue Française. Marseille May 23–25, 1955. President, Professor Paul Giraud. General Secretary, Associate Professor René Bernard, Clinique Médicale Infantile, Hôpital de la Conception, Marseille, France.

Annales Paediatriae Fenniae is a new periodical devoted to problems in the field of pediatrics in Finland, published by the Finnish Medical Society and edited by Professor Arvo Ylppö. The articles in the first issue just out are all written in English. Two Supplements have already been published, by Annikki Seppä-Kivalo (On Seasonal Variation in the Galvanic Excitability of Infants in Finland) and by Irja Salmi (On the Influence of Anoxia on Plasma Calcium). The address for subscription ($ 5 or Swed. crowns 22 per volume) and for all communications is as follows: Annales Paediatriae Fenniae, Kalevankatu 11, Helsinki, Finland.

The Editors of the Acta Pædiatrica extend to this new pediatric review their best wishes.